UNIVERSIDADE D
COIMBRA

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CONTRIBUTION TO THE DEVELOPMENT OF A PREDICTIVE MODEL FOR THE FUNCTIONAL PROGNOSIS OF HEMIPLEGIC PATIENTS

Tese de Doutoramento no âmbito do Programa de Doutoramento em Ciências da Saúde - ramo de Medicina, orientada pelo Professor Doutor João Páscoa Pinheiro e pelo Professor Doutor António Freire Gonçalves e apresentada à Faculdade de Medicina da Universidade de Coimbra.

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Tese apresentada à Faculdade de Medicina da Universidade de Coimbra para candidatura ao grau de Doutor em Ciências da Saúde – ramo de Medicina, realizada sob a orientação científica do Professor Doutor João Páscoa Pinheiro, Professor Doutor João Sargento-Freitas e Professor Doutor António Freire Gonçalves.

AGRADECIMENTOS

Agradecer um projeto como este, multidisciplinar, que juntou competências de diversas pessoas e centros, torna-se uma tarefa obrigatória, mas notoriamente difícil.

A realização do trabalho que conduziu a esta dissertação apenas foi possível devido à conjugação de esforços de uma equipa unida e estruturada, constituída por pessoas com diferentes domínios de conhecimento, às quais aqui dirijo o meu sincero agradecimento.

Ao Prof. Doutor João Páscoa Pinheiro, orientador de tese, agradeço o apoio e confiança que sempre me transmitiu, mas sobretudo o rigor metodológico e profissional. Meu mestre, na formação clínica e científica, nunca o poderei dissociar do meu trajeto profissional. Agradeço a constante partilha de conhecimentos e críticas construtivas que me orientaram durante estes anos.

Ao Prof. Doutor João Sargento-Freitas, além de um mestre, um amigo, que com o seu exemplo de rigor científico e avultada experiência em investigação na área de neurociências, constituiu um esteio fundamental no desenvolvimento e concretização deste trabalho.

Ao Dr. Jorge Laíns, um mestre, uma referência clínica, agradeço a total disponibilidade, a motivação que sempre me soube transmitir. Incutiu um elevado rigor científico ao longo de todo o projeto, tornando-se elemento fundamental na revisão clínica do conteúdo final da tese.

Ao Prof. Doutor Pedro Lopes Ferreira, pela disponibilidade, rigor científico e partilha de elevado saber no domínio da área Economia e Gestão e Ciências da Saúde, elemento fundamental para o sucesso e realização deste projeto científico.

Ao Prof. Doutor Freire Gonçalves, coorientador de tese, agradeço o seu voto de confiança no projeto bem como a sua revisão crítica do conteúdo final da tese.

Ao Prof. Fontes Ribeiro, tutor de tese, agradeço o acolhimento do projeto e importante contributo na revisão crítica do conteúdo final da tese.

À Prof. Anabela Correia Martins, pelo elevado saber e domínio científico, visão sempre crítica do projeto e revisão do conteúdo final da tese.

Um muito especial agradecimento à Dra. Sandra Oliveira e à Dra. Joana Costa, elementos fundamentais para a realização deste projeto.

À equipa de enfermagem da Unidade de AVC e Fisioterapeutas e Terapeutas Ocupacionais do Centro de Medicina Reabilitação Região Centro – Rovisco Pais (CMRRC-RP) pelo apoio incondicional.

Aos restantes colegas e parceiros de investigação do Serviço de Neurologia do CHUC, Biocant e CMRRC-RP pelo companheirismo e ajuda.

Finalmente, uma palavra de agradecimento às Pessoas especiais da minha vida:

Aos meus pais, porque são o meu porto de abrigo, acolhendo-me e incentivando-me sempre com o seu amor incondicional.

À Ana Miguel e ao meu pequeno bebé João, que são o meu Mundo e a minha fonte de motivação todos os dias!

À memória da minha irmã, sempre presente, o meu anjo da guarda que me deu motivação e força para seguir em frente nos momentos de maior adversidade.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ACA:	Anterior Cerebral Artery
ADL:	Activities of daily living
AF:	Atrial fibrillation
AFO:	Ankle-foot orthotics
ASPECTS:	Alberta Stroke Program Early CT Score
AUC:	Area under the curve
BATRAC:	Bilateral arm training with rhythmic auditory cueing
CT:	Computed tomography
CRP:	C-reactive protein
CSF:	Cerebrospinal fluid
DH:	Dominant hemisphere
DGS:	Direção-Geral da Saúde
DM:	Diabetes mellitus
DW-MRI:	Diffusion-weighted MRI
ED:	Emergency department
EMG-stim:	Electromyography-triggered neuromuscular stimulation
EQ-5D:	EuroQol five dimensions questionnaire
FES:	Functional electrical stimulation
FIM:	Functional independence scale
FLAIR:	Fluid-attenuated inversion recovery
GFAP:	Glial fibrillary acidic protein
HF:	Hearth failure
HH:	Homonymous hemianopsia
ICAM 1:	Intercellular adhesion molecule 1
ICD-10:	International Classification of Diseases 10
ICIDH1:	International classification of impairments, disabilities, and handicaps
ICF:	International Classification of Functioning and Disability
IL-6:	Interleukin-6
MBP:	Myelin basic protein
MCA:	Middle cerebral artery
MESUPES:	Motor Evaluation Scale for Upper Extremity in Stroke
MIME:	Mirror image movement enabler
MMP:	Matrix metalloproteinases
MRI:	Magnetic resonance imaging

mRS:	Modified Rankin Scale
NMDA:	N-methyl-d-aspartate
NIHSS:	National Institutes of Health Stroke Scale
NSE:	Neuronspecific enolase
PCA:	Posterior cerebral artery
PEG:	Percutaneous endoscopic gastrostomy
PRM:	Physical and Rehabilitation Medicine
QoL:	Quality of Life
ROC:	Receiver Operator Characteristic
rt-PA:	Recombinant tissue plasminogen activator
rTMS:	Repetitive transcranial magnetic stimulation
S100β:	S100 calcium binding protein β
SENS:	Sensory transcutaneous electrical nerve stimulation
SIS:	Stroke Impact Scale
SULCS:	Stroke Upper Limb Capacity Scale
TD:	Transcranial Doppler
TIBI:	Thrombolysis in Brain Ischemia
TMS:	Transcranial magnetic stimulation
TNF-α:	Tumor Necrosis Factor α
TOAST:	Trial of ORG 10172 in Acute Stroke Treatment
VAS:	Visual analogue scale
VCAM 1:	Vascular cell adhesion protein 1
vWF:	Willebrand factor
WHO:	World Health Organization

LIST OF TABLES

LIST OF ILLUSTRATIONS

PART A

INTRODUCTION

ABSTRACT

Stroke is a major cause of significant morbidity, mortality and disability. Between 15% and 30% of stroke survivors suffer from permanent disability, with 20% requiring institutional care within the 3 months following the acute event. However, most efforts are aimed at predicting vital prognosis instead of functional prognosis.

Approximately 70% of stroke survivors show hemiparesis with brachial predominance in the acute phase, which makes upper limb recovery an important and challenging objective. Anticipating functional prognosis would make it possible to define an adequate, objective and individualized rehabilitation program, with more efficient resource allocation. The challenge of current research is to define a reproducible, sensitive and feasible model that predicts patient functionality.

This work has the main objective of assessing the predictive value of a group of clinical variables and peripheral blood biomarkers, in determining functional prognosis on the short and medium-term after acute stroke. These biomarkers could theoretically be used to develop further reliable instrument, to predict functional prognosis at an early stage.

Two cohorts of patients were included in this work. One cohort was used to validate the Stroke Upper Limb Capacity Scale (SULCS) assessment scale for the Portuguese population. The other, consisting of ischemic stroke patients, was used to develop of a predictive functional model of short- and medium-term prognosis after stroke. Evaluations were made at different time periods in the recovery process, since hospital admission to 6 months after stroke.

When assessing a panel of neuroimaging, serum, and clinical markers, there was evidence of correlation between different markers and patient functionality. We emphasize a National Institutes of Health Stroke Scale (NIHSS) score < 13.5 at admission, an Alberta Stroke Program Early CT Score (ASPECTS) score ≥8 within 24 hours of hospital admission and serum levels of S100β protein <140.5 ng/L at 48 hours after hospital admission, as main predictors of good upper limb functioning. Conversely, advanced age was significantly associated with worse upper limb function 12 weeks after stroke. Upper limb functioning measured in acute stroke phase (48 hours) was strongly correlated with general and upper limb functioning in both short and medium-term (3 and 12 weeks respectively). These findings suggest that SULCS in acute phase can provide a valuable insight for medium-term functional recovery, which needs further investigation. S100β levels were identified particularly as a strong predictor of functional outcome after stroke. Therefore, the clinical utility of S100β as predictor of functional recovery after-stroke should be emphasized in clinical practice and more robust large-scale studies with longer follow-up periods should be conducted to further validate the use of this biomarker.

An integrative model was built to provide relevant insight when predicting medium-term functional prognosis for the upper limb in the post-stroke period. This information can then be used to develop a specific rehabilitation program aimed to ensure that patients reach their maximum rehabilitation potential at a lower cost. This would allow the physician to establish a better resource allocation. Following exhaustive statistical analysis of all variables, we identified a model that uses a combination of three different predictors, including S100β levels, age, and NIHSS score.

This scientific project allowed us to valuably contribute to clinical research in the context of physical and rehabilitation medicine, highlighting the necessity of translational science, which has

paramount importance on building predictive models that integrate the laboratory, clinical and functional components.

Keywords: Functioning; Stroke; Upper limb; Biomarkers; S100β; Predictive models; SULCS

RESUMO

O acidente vascular cerebral (AVC) continua a ser manifestamente uma patologia com significante morbidade, mortalidade e incapacidade. Entre 15% e 30% dos sobreviventes do pós AVC sofrem de incapacidade permanente, sendo que 20% exigem cuidados institucionais nos 3 meses após a lesão. Assiste-se, porém, a um interesse particular na previsão do prognóstico vital em detrimento do prognóstico funcional.

Aproximadamente 70% dos sobreviventes de AVC apresentam na fase aguda hemiplegia de predomínio braquial, o que torna a recuperação do membro superior um importante e desafiante objetivo. Antecipar o prognóstico funcional permitiria definir um programa de reabilitação adequado, objetivo e individualizado, com uma alocação de recursos mais eficiente. O grande desafio da investigação atual é definir um modelo reprodutível, sensível e exequível, preditor da funcionalidade do doente.

Este trabalho teve como objetivo avaliar o valor preditivo de um conjunto de variáveis clínicas e biomarcadores no sangue periférico para determinar o prognóstico funcional a curto e médio prazo em doentes com AVC numa fase aguda. Estes seriam utilizados para o desenvolvimento de um instrumento fiável a ser aplicado na prática clínica com o propósito de determinar precocemente o prognóstico funcional destes doentes.

Foram incluídos dois coortes de doentes. Um primeiro coorte foi utilizado para validar a escala *Stroke Upper Limb Capacity Scale* (SULCS) para utilização na população portuguesa. O segundo coorte, constituído por doentes com AVC isquémico, teve como objetivo o desenvolvimento de um modelo preditivo da funcionalidade do membro superior e funcionalidade global, a curto e médio prazo em doentes com AVC. A avaliação dos doentes efetuou-se em vários tempos do processo de recuperação do evento agudo, desde a admissão hospitalar até aos 6 meses após AVC agudo.

Ao avaliar um painel de marcadores clínicos, serológicos e de neuroimagem, alguns destes mostraram correlação com a funcionalidade dos doentes ao longo do processo de recuperação funcional. Destacámos assim no nosso estudo como principais preditores de boa funcionalidade do membro superior às 12 semanas após o AVC a pontuação à admissão na unidade de AVC na escala *National Institutes of Health Stroke Scale* (NIHSS) < 13,5 , a pontuação da escala *Alberta Stroke Program Early CT Score* (ASPECTS) ≥8 nas primeiras 24 horas após a admissão hospitalar e os níveis séricos de proteína S100β <140,5 ng/L às 48 horas após a admissão hospitalar. Por outro lado, a idade avançada foi significativamente associada com pior funcionalidade do membro superior 12 semanas após o AVC. A funcionalidade do membro superior medida na fase aguda do AVC (às 48 horas) foi fortemente correlacionada com o funcionalidade geral e funcionalidade do membro superior após o AVC tanto a curto como a médio prazo (3 e 12 semanas). Estes resultados sugerem que a pontuação SULCS na fase aguda do AVC pode fornecer informações valiosas para a recuperação funcional a médio prazo, o que justifica a investigação em estudos futuros. O nível sérico da proteína S100β foi particularmente identificado como um biomarcador de funcionalidade após o AVC. A utilidade clínica da S100β como um preditor de recuperação funcional após o AVC deve ser enfatizada na prática clínica, todavia estudos mais robustos, de maior dimensão e com períodos de acompanhamento mais longos, deverão ser realizados para a validação adicional deste biomarcador.

Procurou-se a criação de um modelo integrativo para fornecer informações relevantes com vista à previsão do prognóstico funcional a médio-prazo para o membro superior no período pós-AVC. Esta informação poderá ser usada, desde o início, numa abordagem personalizada do programa de reabilitação, com o objetivo de garantir que os doentes podem atingir o seu potencial máximo de reabilitação de forma mais rápida e com custos mais baixos, permitindo ao clínico uma mais eficiente alocação dos recursos. Após a análise estatística exaustiva de todas as variáveis em estudo, identificamos um modelo usando a combinação de três preditores diferentes, nível da proteína S100β, idade e a pontuação na escala NIHSS.

Este projeto científico permitiu-nos contribuir de forma valorosa para a investigação clínica no contexto da medicina física e reabilitação e destacar a necessidade e o valor acrescentado da ciência translacional, que é fundamental na construção de modelos preditivos que integrem os conteúdos laboratoriais, clínicos e funcionais.

Palavras-chave: Funcionalidade; AVC; Membro superior; S100β; Modelos preditivos; SULCS

THESIS OUTLINE

This thesis is divided in four 4 parts:

Part A – Includes the abstract, the list of publications arising from this thesis, and defines the purpose of this dissertation. Then provides an overview of the state of the art in the field of physical and rehabilitation medicine and, specifically functional recovery after acute stroke.

Part B – Presents the specific aims of this thesis culminating from the current evidence gaps that need to be addressed to improve functional recovery after stroke. The specific hypotheses laid out for this thesis and the study methodology used to test those hypotheses is also described in this section.

Part C – Presents the results of the experimental work conducted in the context of this thesis. This section consists of 6 different chapters, shown in the manuscript format submitted/accepted when publishing those findings in international medical journals. Chapter 4 presents a literature review of the role of neuroimaging and blood biomarkers in the functional prognosis after stroke. Chapter 5 describes the process of transcultural adaptation and validation of the Portuguese version of the Stroke Upper Limb Capacity Scale. Chapter 6 addresses the role of S100β protein as a predictor of post-stroke functional outcome. Chapter 7 evaluates a panel of neuroimaging, serum biomarkers, and patient characteristics as predictors of upper limb functioning 12 weeks after acute stroke. Chapter 8 details the process of functional recovery in the first 6 months after acute ischemic stroke. Chapter 9 evaluates, specifically, the impact of post-stroke recanalization on general and upper limb functioning.

Part D – Integrates the results of the experimental work, providing an integrative model aiming at predicting upper limb function after stroke in Chapter 10. Lastly, in Chapter 11, the overall conclusions on the results of this research project are discussed, as well as possible lines of future research.

References – Provides general references for Part A, B, and D. References of part C are contained within each chapter in manuscript form.

DISSERTATION PURPOSE STATEMENT

Stroke is still a condition leading to substantial morbidity, mortality and disability. Approximately 70% of stroke survivors present incomplete hemiplegia of brachial predominance, which makes the recovery of upper limb functioning a relevant and challenging therapeutic goal [1–4].

Better tools to establish the prognosis of stroke patients are highly relevant for both clinicians and researchers, but current models are insufficient to accurately determine functional prognosis after stroke, since most studies have historically focused on vital prognosis in the acute phase. More recently, some attention has been devoted to functional outcome, however it is still based on limited assessments, leaving important capacities such as upper limb use devoid of specific evaluations [5–7].

The reliability of current models could possibly be improved by identifying accurate blood markers of pathological processes involved in acute ischemic stroke (inflammation, hemostasis, neuronal or glial damage, and cardiac dysfunction), examining demographic factors, developing and validating reliable metric instruments for the acute phase, using the most sensitive and specific imaging exams and scoring systems [8–10].

This work aims to determine the predictive value of an assembly of demographic/clinical factors, biomarkers, and imaging techniques for short- and medium-term functional prognosis in patients with acute stroke. These data will provide valuable insight in developing an instrument which can be applied in clinical practice as an early predictor of functional prognosis in acute stroke patients. Ultimately, the formulation of an objective, reproducible, sensitive, and feasible clinical model will allow early screening of patients to tailor rehabilitation programs, controlling resources and leading to better functionality.

There is an increasing need to produce evidence in the context of physical and rehabilitation medicine, which has become a responsibility for clinicians and other professionals in the area. This work is aimed at providing added value for both clinicians and patients.

PUBLICATIONS ARISING FROM THIS THESIS

Review

Neuroimaging and Blood Biomarkers in Functional Prognosis after Stroke
João Paulo Branco, Joana Santos Costa, João Sargento-Freitas, Sandra Oliveira, Bruno Mendes, Jorge Laíns, João Pinheiro
Acta Med Port 2016 Nov;29(11):749-754 DOI:10.20344/amp.7411

Original Research

Assessing upper limb function: transcultural adaptation and validation of the Portuguese version of the Stroke Upper Limb Capacity Scale
João Paulo Branco, Sandra Oliveira, João Páscoa Pinheiro and Pedro L. Ferreira
BMC Sports Science, Medicine and Rehabilitation (2017) 9:15 DOI 10.1186/s13102-017-0078-9

S100β protein as a predictor of post-stroke functional outcome: a prospective study
João Paulo Branco, Sandra Oliveira, João Sargento-Freitas, Joana Santos Costa, Gustavo Cordeiro, Luís Cunha, António Freire Gonçalves, João Pinheiro
J Stroke Cerebrovasc Dis. 2018 Jul;27(7):1890-1896.
DOI: 10.1016/j.jstrokecerebrovasdis.2018.02.046

Neuroimaging, serum biomarkers, and patient characteristics as predictors of upper limb functioning 12 weeks after acute stroke: an observational, prospective study
João Paulo Branco, Sandra Oliveira, João Sargento-Freitas, Orlando Galego, Gustavo Cordeiro, Luís Cunha, António Freire Gonçalves, João Pinheiro
Top Stroke Rehabil. 2018 Sep 13:1-7. DOI: 10.1080/10749357.2018.1517491.

Assessing functional recovery in the first 6 months after acute ischaemic stroke: a prospective, observational study
João Paulo Branco, Sandra Oliveira, João Sargento-Freitas, Jorge Laíns, João Pinheiro
Eur J Phys Rehabil Med. 2019 Feb;55(1):1-7. DOI: 10.23736/S1973-9087.18.05161-4.

Impact of post-stroke recanalization on general and upper limb functioning: a prospective, observational study
João Paulo Branco, Filipa Rocha, João Sargento-Freitas, Gustavo Cordeiro, António Freire, Jorge Laíns, João Páscoa Pinheiro
Submitted: BMJ Neurology

CHAPTER 1

BACKGROUND

Physical and Rehabilitation Medicine

The medical specialty of Physical and Rehabilitation Medicine (PRM) is primarily responsible for the diagnosis, prevention, treatment, rehabilitation, and integration of individuals functionally affected by disease, trauma or disability in all ages and both in acute and chronic settings [11]. PRM addresses impairments and activity limitations in order to facilitate patients' physical and cognitive functioning, participation, and modifying personal and environmental factors [11].

PRM cannot be defined according to the biomedical model used for most medical specialties. In addition to an adequate approach in the examination and assessment of functionality as well as the use of proper technology, PRM is based on a philosophy of medical responsibility (biopsychosocial model).

PRM as a field of specialization strives to improve functioning of people with a health condition or disability. Thus, the main goal of PRM is to contribute to the rehabilitation/recovery of individuals with functional impairment, with a scientific approach. In this context, PRM requires autonomous, specific training and an organization that allows the PRM specialist to support other specialties, with a global but also differentiated approach. Therefore, in PRM teamwork is paramount, with multidisciplinary and multiprofessional teams.

Scientific research is essential in advancing PRM, but researchers face challenges in developing research projects due to the inherent heterogeneous populations and medical conditions, as well as the need for personalized interventions. In this context, entire teams should be involved in research projects to allow the implementation of more ambitious methodologies that can provide greater insight into how to better improve patient outcomes [12, 13].

Rehabilitation and the role of Physical and Rehabilitation Medicine

Improvements in the living conditions among modern societies, medical-surgical advances, and the promotion of healthcare services allowed substantial increases in longevity, with a subsequent increase in the number of older individuals. This increase in life expectancy led to a new medical and social phenomenon: chronicity, the progressive increase on chronic diseases in the population, often disabling diseases.

Technological developments seen in the last decades along with changes in the lifestyle and everyday rhythm lead to a growing number of people with disability and consequent restriction in participation. These levels of disability are a result of traffic accidents, workplace accidents as well as several pathologies (e.g. cerebrovascular and cardiovascular conditions) and occur at increasingly younger and productive ages. Advances in medicine and healthcare allow the survival of increasing numbers of people that would otherwise die, but disability is a frequent consequence that needs to be addressed.

The need for rehabilitation care arises with a demand for increasingly early and rapid response in the acute and sub-acute phases. There is an increasing need to support more severe and disabling cases, in an aging population with a growing number of very old individuals.

In these populations, early intervention from PRM is of fundamental relevance, along with the specific interventions of the different medical specialties. After that period, in cases where significant disability persists and there is a potential for rehabilitation, PRM has a dominant role. Here, the

continuity of rehabilitation care is paramount and should be provided in a timely manner, avoiding delays and interruptions that may compromise recovery. The ultimate goal is to reduce sequelae that may compromise future quality of life as much as possible, by promoting and enhancing functionality, physical and phycological recovery through adequate therapeutic programs, with multidisciplinary approaches. This allows the individual to reach the maximum rehabilitation potential and, thus, attain independence in activities of daily living (ADL) and, consequently, family, occupational, and social re-insertion.

Rehabilitation is therefore relevant for most medical specialties, particularly in the presence of potentially debilitating and disabling conditions. Rehabilitation changes the old clinical concept that considered the clinician's mission ended when the acute affection was controlled or healing was achieved. The subsequent phase of convalescence or recovery should be seen as its own medical domain, as it is highly relevant for the future of the patient.

Rehabilitation is effective in reducing the burden of disability and increasing opportunities for disabled individuals. The associated costs are usually lower than what would have to be supported by healthcare systems if rehabilitation care was not available.

Over the years, rehabilitation has been seen as the strategic health approach for the 21st century in addition to prevention and treatment. But nowadays, with the objective of optimizing the health potential of the individual, this vision evolved towards the integration of the three components. The goal is to maximize the potential benefits of rehabilitation interventions, at physical, cognitive and motivational levels, promoting functional independency by following a model of early intervention, which is initiated during the acute phase in the context of hospitalization.

After this phase, continued care must follow, according to the concept of care continuum, which encompasses all subsequent stages, from hospital admission to discharge. It includes rehabilitation in the acute phase (including rehabilitation during hospitalization) and rehabilitation in ambulatory and eventual need for maintenance care (at home or in adequate healthcare units). Looking for better solutions in the promotion and maintenance of health among individuals with disability specific healthcare services were developed or restructured. Institutions aimed at facilitating patient re-adaptation and socio-professional re-integration were also created. This vision of rehabilitation requires the integration of rehabilitation care in the intensive care units, in acute care wards, in ambulatory care, in home care, and in continued and palliative care.

The evolution of the patient condition through the rehabilitation program is not simple nor linear. The expectations of the patient and family members should be established based on a realistic functional prognosis and an acceptable time interval, following adequate clinical evaluation, within a tailored rehabilitation program that is periodically evaluated, namely through the use of adequate assessment tools (Figure 1.1).

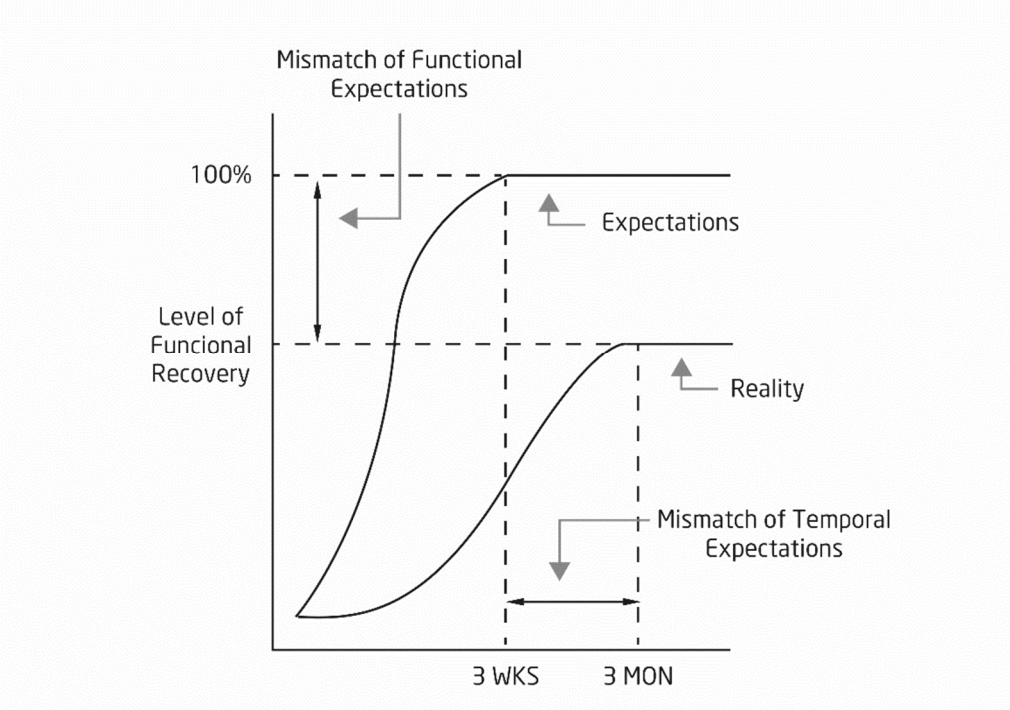

Figure 1.1 – Evolution of patient expectations during the rehabilitation program.
Adapted with permission from: Krusen's Handbook of Physical Medicine and Rehabilitation, 4th ed.

The plateau of functional gains and the transition from a "medical-rehabilitation" phase to a "social" phase with the need for maintenance rehabilitation care is still an area of controversy and possible and desirable discussion. PRM is perhaps the most social of all medical specialties and the palliative role of rehabilitation should be questioned, assumed and valued. It is in this broad concept that rehabilitation is developed and can provide the greatest value. For its full realization, its actions should encompass the most diverse areas, including health, education and training, employment, social security, environmental control, sports and leisure.

Models of disability

Several models of disability were developed over the years and have influenced policy, practice and research guidelines, with a relevant impact on PRM. From an initial vision of disability based on a cultural perspective without an objective and scientific basis (i.e. the traditional model), we have seen an evolution towards a model based on scientific evidence and supported by medical practice and knowledge. Disability started to be seen as an intrinsic issue of the individuals and was mainly valued considering the physical limitations (i.e. the medical model). Later, the social model was developed, based on the expectations of the individuals with disability and in which disability started to be seen as an issue that goes beyond the physical limitations, representing an issue for society and focusing on the rights of individuals with disability. Nowadays, an integrational model, which integrates the approaches of the medical and social models is the preferred approach. Here, medical and scientific knowledge is taken together with the experiences of people with disability, integrating all the dimensions of disability and thus, approaching it more comprehensively.

In 1965, the World Health Organization (WHO) presented the Saad Nagi model as a first organized way of interpreting the consequences of active pathology and its negative impact on functionality [14–17] (Figure 1.2). The structural concepts in this model are "active pathology", "physical impairment", "functional limitation" and "disability". Disability is described in the Nagi model as the ultimate consequence of active pathology and identified in relationship with the environment. It proposes a comprehensive and systematic effort directed at functionality, particularly at the performance of ADLs. The term "active pathology" is an interruption or interference with normality and with repair efforts, the "physical impairment" is an anomaly or loss in anatomy, physiology, organ or function, "functional limitation" is seen as a limitation in the individual's performance, and "disability" is a limitation of the function considered normal for that individual [14–17].

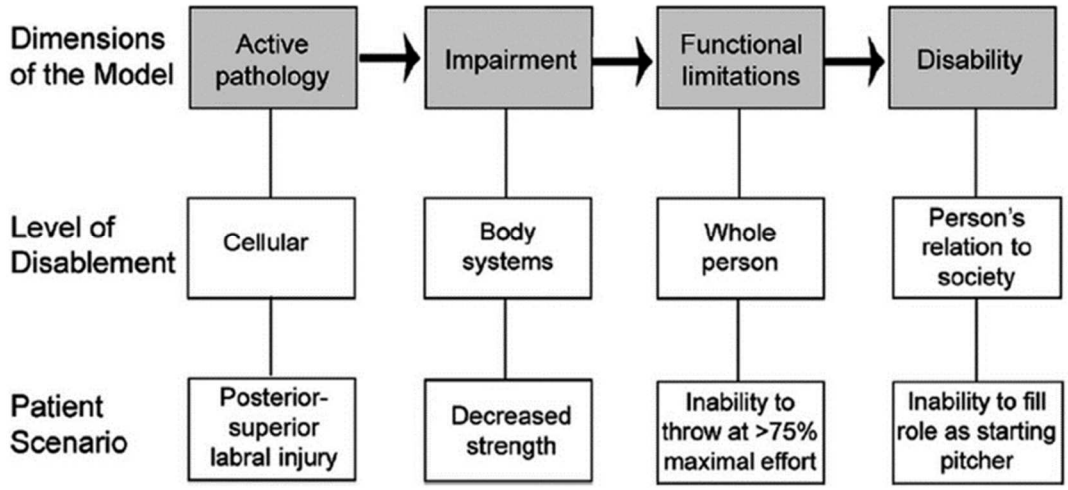

Figure 1.2 – The Nagi Model of Disability.
Adapted with permission from Cheville AL, Morrow M, Smith SR, Basford JR. re. PM R 2017 Sep;9(9S2):S335–46.

The WHO further presented, in 1980, the International classification of impairments, disabilities, and handicaps (ICIDH1) model, which incorporates as structuring concepts "disease", "impairment", "disability", and "handicap". The ICIDH1 model was developed among others by P. Wood [16]. Impairment is seen as loss of substance or alteration of function or an anatomical, physiological or psychological structure (tissues and organs). Disability is a partial or total reduction of the capacity to perform a task or an activity in the limits considered acceptable for the species. The handicap is seen as the social prejudice, is a limitation preventing or making it more difficult to represent a given role in the environment and in society. The ICIDH1 model introduces the concept of "handicap" or "disadvantage" as the last to characterize the consequences of diseases, not as an individual denomination but as a classification of circumstances [14, 16, 17]; it is a question of formulating a framework in the environment, a multifactorial social phenomenon. Different variables contribute to the understanding of this dimension, namely orientation, physical independence, mobility, occupation

of time, social integration and economic self-sufficiency [14, 16, 17]; a disability becomes disadvantageous when some of the environment variables are altered.

The WHO introduces in 1999-2000 the ICIDH2 model where the structural concepts “active pathology”, "impairment", "activity" and "participation". Deficiency refers to the level of the body, characterized in structure and function and presenting the loss of function as the main negative factor. Activity refers to the level of the Person and is characterized by the possibility of performing a set of tasks (ADLs) and the limitation/restriction of this activity is the negative factor. Participation, considered at the social level, is a willingness to be involved in a given situation, and the main negative factor is the impairment or restriction to this involvement. The ICIDH2 model that evolved according to the foundations of ICIDH1 (1980) that considers as consequences of disease three levels, associated to contextual factors of the individual and the environment. The intrinsic factors are age, genetic load, existing pathologies, while the extrinsic factors are the environmental factors including architectural barriers (stairs, narrow doors, elevated walkways, ...). At the risk of semantic inaccuracy or reductive identifications, we can say that we reeducate impairment, rehabilitate disability, and readapt/ reintegrate/ include the disadvantage.

The revision of the interpretive models for the consequences of disease (final version of May 2001) [18] establishes a new name, "The International Classification of Functioning and Disability", with the acronym ICF (Figure 1.3); it also aims to end the negative emphasis on describing levels (impairment, disability and disadvantage) and promoting a more optimistic way of classifying in function [18, 19]. The role of environmental factors is increasingly emphasized, particularly in relation to function and disability, as well as the impact of the physical and social environment on the understanding of health status. ICF represents a WHO effort to interpret planetary concerns in health and in particular in function; contemplates a change of paradigm, by starting to classify health components and not consequences of disease [19]. The ICF also establishes several analogies and complementarities with the International Classification of Diseases 10 (ICD-10); the ICD-10 allows a diagnosis of diseases, disorders or other health conditions, while the ICF illustrates the functional condition and the expression of disability.

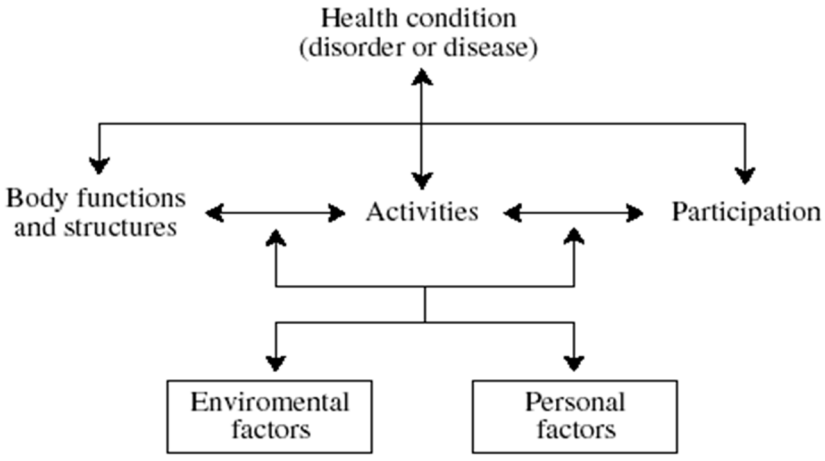

Figure 1.3 – ICF framework of functioning and disability.

Adapted with permission from European Physical and Rehabilitation Medicine Bodies Alliance. White Book on Physical and Rehabilitation Medicine (PRM) in Europe. Chapter 1. Definitions and concepts of PRM. Eur J Phys Rehabil Med 2018;54:156-65

The thematic contents of the ICF are organized according to two interest groups, functionality / disability and contextual factors; the first group includes the body component (function and structure) and the activity and participation component, while the second group is divided between the environmental and personal factors already discussed. The various components can be addressed in positive or negative, facilitating or inhibitory terms [19, 20]. Thus, according to ICF, "body function" is the physiological function of a system or organ, "structure" is an anatomical component, "disability" is a deviation or a loss in function or structure, "activity" is the execution of a task or action and "participation" is the commitment to everyday life.

The ICF, thus, integrates the biomedical model, considered traditional (care and teaching) with the biopsychosocial model. In the biomedical model disability is something exclusively inherent to the patient, something individual and restrictive; in the biopsychosocial model, disability is a multifactorial condition determined by society. Functionality emerges as a dominant idea, given the human being's need to interact with space and time; it is about changing the paradigm, built on respect for the rights of the citizen, a perspective of inclusion and the right to life.

Neurological disease as cause of disability

Neurological disease, and particularly cerebro-vascular disease, is one the main causes of disability in western societies. This leads to the need for adequate PRM services, Specialized Rehabilitation Centers, as well as all the care continuum resources available to the patients, while ensuring sufficient resources and links between different levels of services.

According to the Direção-Geral da Saúde (DGS), in 2014 the number of hospital discharges with the diagnosis of ischemic stroke, intracranial, subarachnoid and intracerebral bleeding was 25,056 (see Table 1.1).

Table 1.1 – Hospitalizations due to cerebrovascular disease.

Main diagnosis	Discharged patients	Deaths	Mean hospitalization time	Day Cases	Mean hospitalization time without Day Cases
Occlusion of cerebral arteries/ ischemic stroke	19,797	2286	12.55	175	12.66
Intracerebral hemorrhage	3713	1068	14.54	65	14.79
Subarachnoid hemorrhage	713	144	18.91	25	19.59
Intracranial hemorrhage NCOP	833	116	13.48	24	13.88
Total	25,056	3614			

Source: Adapted from “Direção-Geral da Saúde. (2015). Portugal – Doenças Cérebro-Cardiovasculares em Números – 2015.

Data from the European Stroke Organization indicate that 30-day mortality associated with stroke varies substantially according to etiology, with a mortality of 8-15% in ischemic stroke, 42-46% in subarachnoid hemorrhage and 48-82% in intracerebral hemorrhage. The incidence of stroke increases with age, 15% of strokes occur in individuals younger than 50 years old and 25% in individuals younger than 65 years old.

According to 2011 data from the National Stroke Association, 10% of stroke survivors recover almost fully, 25% recover with minimal sequelae, 40% have moderate to severe disability requiring specialized care, 10% required long-term care leading to institutionalization, and 15% die within 30 days of the acute episode [21]. Data from the UK also show a similar pattern, indicating that 50% of stroke survivors have some degree of disability, 33% are dependent in their daily living, and mortality after 30 days is 12.5% [21].

Stroke

Stroke is a major public health issue worldwide, since it constitutes the third most frequent cause of death and permanent disability in developed countries [22]. In Portugal, the impact of stroke is even higher, since it is the first overall cause of death and disability [23].

Stroke remains an important cause of functional disability, with particular impact among individuals over 65 years-old [3]. Up to 30% of stroke survivors endure permanent disability, with approximately 20% requiring inpatient care during the first 3 months after the acute episode [1]. In the acute phase, most patients that survive stroke present hemiparesis of brachial predominance, which requires inpatient care in a substantial proportion of cases [1]. Since neuroplasticity after stroke is higher in the first 12 weeks after the acute ischemic lesion, there is a limited window for intervention towards patient recovery [24].

Therefore, measures of functional prognosis after stroke are of great interest for both clinicians and researchers. Early diagnosis and identification of stroke etiology in predicting the likelihood of recovery of multiple deficits [25]. The ability of anticipating functional prognosis in the acute phase would allow the development of an adequate rehabilitation program with individualized interventions that could lead to more efficient resource allocation. However, current classification models—based on stroke etiology—are still insufficient to accurately predict functional prognosis [26]. The reliability of such models can potentially be improved using serum biomarkers (inflammation, hemostasis, neural or glial lesion, and cardiac disfunction) and neuroimaging [27]. The main challenge of current research is to define a reproductible model, with good sensitivity and specificity, and which can be feasibly applied in clinical practice as an accurate predictor of patient functionality.

Epidemiology

Stroke is one of the main causes of morbidity and mortality worldwide [28]. The mortality associated with stroke has been reduced in recent years, but the absolute number of stroke events did not decrease, which can be explained by aging populations and a rise in the prevalence of cardiovascular risk factors [29, 30].

In Portugal, 6 strokes are estimated to occur per hour, with 2–3 of those leading to death [31]. The overall incidence is estimated at 1.9%, with higher incidence in males and older adults (65–74 years old) [31]. Although the mortality of stroke has been reduced by half since the year 1990, cardiovascular disease is still the main cause of death in the country (accounting for 35% of deaths), and stroke continues to be greater contributor to this mortality rate than ischemic heart disease [22].

Risk factors

Numerous risk factors have been associated with stroke. The main non-modifiable risk factors include age (risk doubles every decade after 55 years of age), race (greater risk in black individuals, followed by Caucasians and Asians), gender (greater risk in males), family history of stroke, and previous stroke [32, 33].

The modifiable risk factors deserve greater focus from the scientific and healthcare community, contributing to the prevention of acute stroke events. Among the modifiable risk factors, hypertension is perhaps the most prevalent with systolic pressure >140 mmHg and diastolic pressure >90 mmHg representing a higher risk of stroke [32, 33]. Heart disease and heart failure are also major modifiable risk factors, that double the risk of stroke [32, 33]. Atrial fibrillation and valvular heart disease both lead to increased thrombus formation, increasing the risk of stroke [33]. Diabetes also doubles the risk, and glycemic control is not proven to actually reduce the risk of stroke [32, 33]. On the other hand, statins have been established as effective in reducing the risk of stroke, both in patients with or without dyslipidemia [33]. The role of obesity, diet, and sedentarism is not fully elucidated, although it is thought to have a substantial contribution [32]. Additionally, other modifiable risk factors have been described including hypercoagulability states, carotid stenosis, migraine, smoking, alcoholism, sleep apnea, patent foramen ovale, pregnancy and the postpartum period [32, 33].

Types of stroke

When considering its etiology, stroke can be classified as ischemic (87%, thrombolic or embolic) or hemorrhagic (13%, intracerebral or subarachnoid) [32, 33]. The thrombotic occlusion of large vessels (32% to 48% of cases) arises as a consequence of atherosclerotic cerebrovascular disease and/or hypertension, and the associated clinical condition usually has a gradual onset [32, 33]. On the other hand, occlusions in deep penetrating vessels (13% to 18% of cases) lead to lacunar infarcts, causing subcortical deficits [32, 33]. Embolic events (26% to 32% of cases) may arise in the presence of cardiac thrombi (atrial fibrillation, artificial heart valves), paradoxical embolism or unstable atherosclerotic plaques [32, 33]. Paradoxical emboli originate from venous thromboses and reach the left heart circulation (and consequently cerebral arteries) by intracardiac communication in the presence of foramen ovale [33]. The clinical condition has an abrupt onset with a variable evolution due to the possibility of spontaneous thrombus lysis and fragmentation [33].

Importantly, one of the most widely used sub classification system for ischemic stroke is the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, which characterizes both the etiology and the mechanism of lesion. The subtypes defined by this classification include: Large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, and

stroke of undetermined etiology [34]. Approximately 60% of all new ischemic stroke episodes are classified as large-artery atherosclerosis, cardioembolism, or small-vessel occlusion [26].

Intracerebral hemorrhagic stroke arises mostly due to microaneurysm rupture in the penetrating arteries in patients with chronic hypertension [32, 33]. Clinically, patients typically present with acute headache and rapidly developing neurological deficits, whose severity is correlated with the extent of cerebral hemorrhage and edema [32, 33]. Other symptoms include vomiting, neck stiffness, and seizures [32]. Subarachnoid hemorrhages usually result from ruptures of arterial aneurysms located at the base of the skull [32, 33]; these can lead to signs of meningeal irritation and seizures [32, 33]. Arteriovenous malformations can cause subarachnoid hemorrhagic stroke in younger individuals; in a third of cases, seizures or chronic migraine develop prior to stroke [33]. Figure 1.4 summarizes the different causes of stroke and Figure 1.5 summarizes the clinical characteristics of stroke based on the affected territories.

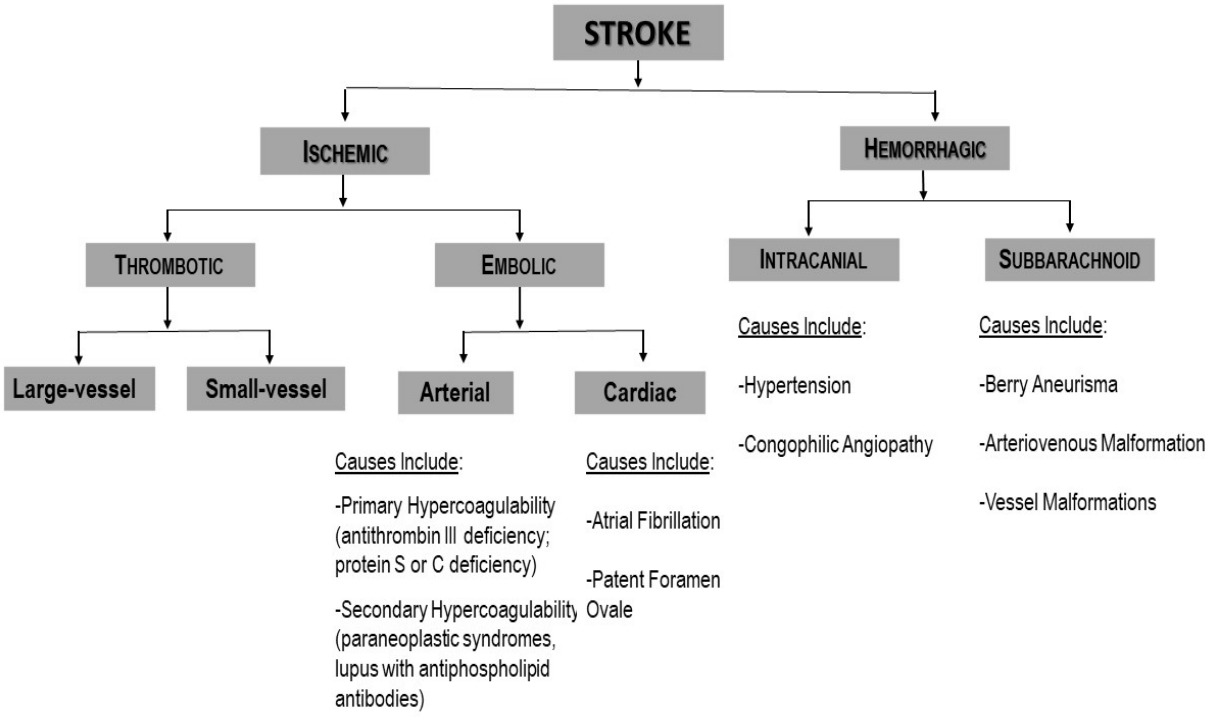

Figure 1.4 – Causes of different types of strokes.

Source: Copyright is with the principal investigator, presented at: 5th Baltic and North Sea Conference on Physical and Rehabititation Medicine & North Sea Conferences on PRM, Maastricht 2017.

Cerebral Vascular Territories

The relationship between the affected vascular territories and the anatomical location of the cerebral functions determines different clinical pictures, each requiring a specific approach from clinicians and other healthcare professionals.

Anterior Cerebral Artery Syndrome (ACA)

The vascular territory of the Anterior Cerebral Artery (ACA) includes the median and paramedian region of the frontal cortex and the lateral region of the hemisphere along the antero-superior border. The deep penetrating vessels irrigate the head of the caudate nucleus and the anterior arm of the inner capsule [33].

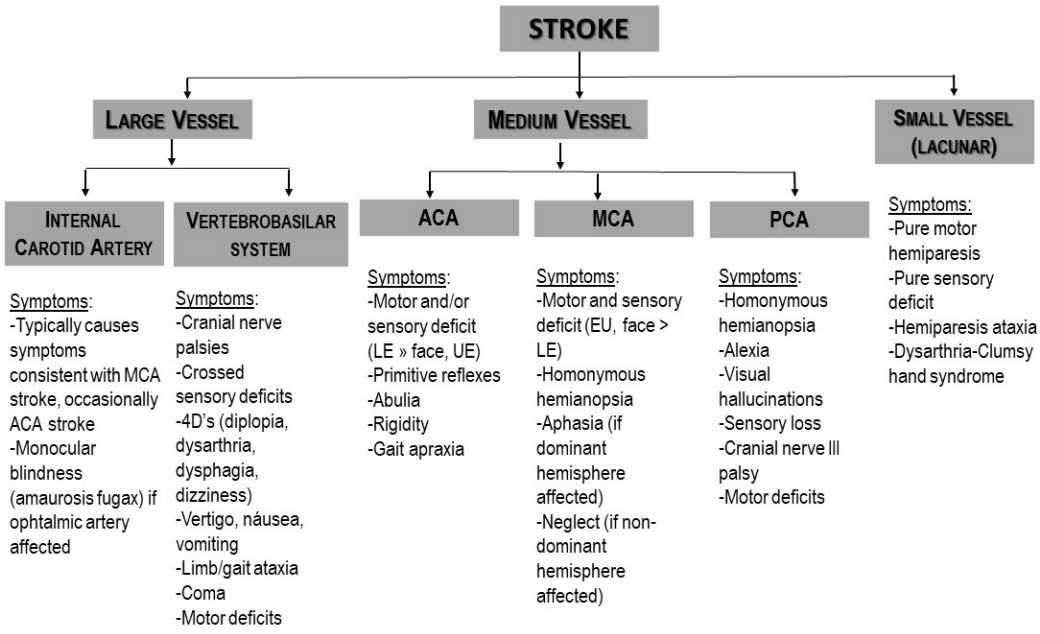

Figure 1.5 – Clinical characteristics of stroke dependent on vascular territory affected.

ACA, anterior cerebral artery; LE, lower extremity; MCA, middle cerebral artery; PCA, posterior cerebral artery; UE, upper extremity. Source: Copyright is with the principal investigator, presented at: 5th Baltic and North Sea Conference on Physical and Rehabititation Medicine & North Sea Conferences on PRM, Maastricht 2017.

Proximal occlusion is well tolerated by the contralateral ACA vascularization [29]. Distal occlusion, on the other hand, results in hemiparesis and contralateral hemihypoesthesia of crural predominance [29, 33]. Frontal lesion leads to reappearance of primitive reflexes (grasp and suction), paratonic rigidity is and, in extensive lesions, behavioral changes such as easy distraction and loss of logical reasoning [29, 33]. Injury to the dominant hemisphere (DH) may cause transcortical motor aphasia [29, 33]. There may be ocular-cephalic deviation towards the side of the lesion and urinary incontinence [29].

Middle Cerebral Artery (MCA) Syndrome

Occlusion of the upper branches of the MCA (Rolandic and pre-Rolandic areas) results in a contralateral sensory and motor deficit in the face, upper limb—and, to a lesser degree, lower limb—oculocephalic deviation to the side of the lesion, Broca's aphasia, spatial deficit, and apraxia [26] (Figure 1.6). The inferior branches irrigate the parietal and temporal lobes, originating contralateral homonymous hemianopsia or superior quadrantanopia [32, 33]. Lesions in the dominant hemisphere

result in Wernicke's aphasia, while HND results in visuospatial deficits with contralateral neglect, apraxia, and aprosodia. Sensory and motor function do not present clinical changes [32, 33]. Occlusion of the MCA in its emergence results in complete hemiplegia, decreased sensitivity, and contralateral hemianopsia [33].

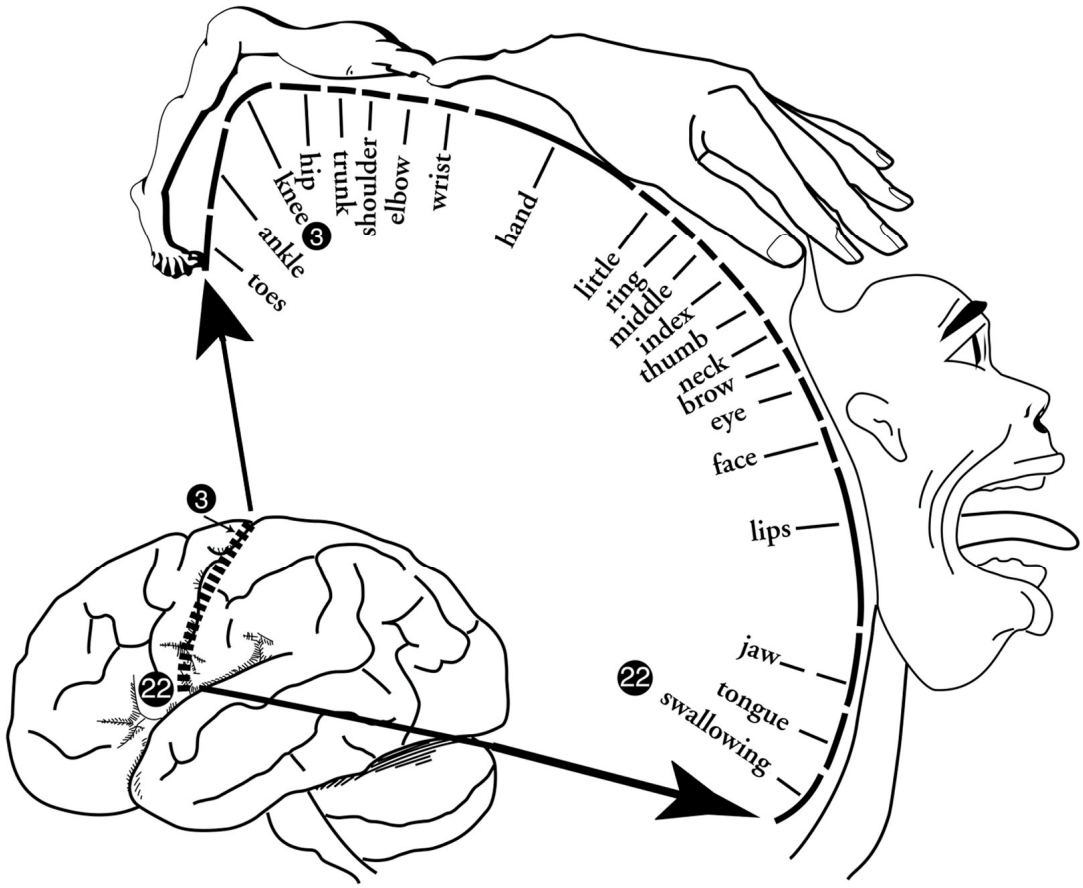

Figure 1.6 – Representation of the body over the primary motor and sensory cortex.

This explains greater arm involvement in a middle cerebral artery occlusion and a greater leg involvement in an anterior cerebral artery occlusion. Source: Adapted with permission from Teasell R, Hussein N, Viana R, et al. Stroke Rehabilitation Clinician Handbook. 2016.

Posterior Cerebral Artery (PCA) Syndrome

The posterior cerebral artery (PCA) is responsible for irrigation of the thalamus, the medial region of the occipital lobe, and the inferior region of the temporal lobe [29, 33]. Occlusion can lead to contralateral hemianopia, prosopagnosia, palinopsia and, if the lesion is located in the DH, alexia and transcortical aphasia [33]. Occlusion of the interpeduncular branches results in Weber's syndrome (oculomotor nerve paresis with contralateral hemiplegia) and paresis of the trochlear nerve [29].

Vertebrobasilar syndrome (VBS)

The vertebral arteries and the resulting basilar artery irrigate the brainstem, cerebellum, and spinal cord [29, 33]. They are characterized by communication with the contralateral vascularization, which translates into the resulting deficits: asymmetric bilateral sensorimotor deficits (ipsilateral in the face and contralateral in the remaining hemibody) and signs of cerebellar involvement [29, 33]. Signs of ipsilateral involvement of cranial nerves, dysarthria, dysphagia, ataxia, vertigo, nystagmus, and Horner syndrome may arise [29, 33].

One of the most noteworthy vertebro-basilar syndromes is the Wallenberg syndrome, which arises by occlusion of the vertebral or posterior inferior cerebellar artery [33]. On the ipsilateral side to the lesion it originates Horner's syndrome, thermal hypoesthesia of the hemiface, and peripheral ataxia with fall to the side of the lesion [29, 33]. Other signs may also arise including thermal hypoesthesia of the contralateral hemisphere, dysphagia, dysarthria and dysphonia (paresis of the palate and vocal cords), diplopia, nystagmus, vertigo, nausea and vomiting (vestibular nucleus) [33]. Occlusion of the basilar artery causes ischemia of the brainstem, which in an extensive lesion leads to Locked-in syndrome (tetraplegia with motor aphasia, with preserved sensibility, comprehension, vision and hearing) [29, 33].

Diagnosis — Stroke assessment tools

Brain imaging techniques gained an increasingly important role in the diagnostic workup of acute stroke patients, constituting an important basis to guide clinical intervention. Computed tomography (CT) is the most widely used imaging technique to evaluate stroke patients in the acute care setting, as it allows the exclusion of intracranial hemorrhage prior to administering antithrombotic treatment [8, 9].

Increasingly, complementary assessment techniques have been developed and introduced in routine clinical practice. Transcranial Doppler Ultrasound (TD) allows the assessment of intracerebral blood flow, which can be used to detect intracranial vascular occlusions, as well as monitoring treatment effectiveness [10]. Conventional cerebral angiography remains, nonetheless, the most specific and sensitive imaging technique in the first 6 hours to visualize MCA occlusions, but since it is an invasive technique its use in not recommended in screening [8, 9]. Brain magnetic resonance imaging (MRI) can also provide valuable information, namely in the identification of brain lesions, particularly when Diffusion-weighted MRI (DW-MRI) is used, as the extent of tissue damage identified by DW-MRI has prognostic value and, therefore, provides valuable insight to guide clinical intervention [35, 36]. In chapter 4, the use of the various neuroimaging techniques as potential predictors of functional prognosis is further explored.

Imaging of the cerebral parenchyma in patients with stroke is a topic of particular clinical interest, and the interpretation of imaging results is now crucial for clinical intervention. Computed tomography (CT) is currently the most widely used imaging technique in evaluating stroke patients during the acute phase. Over the years, efforts were made to allow the standardization of the interpretation of neuroimaging results. One the most widely recognized efforts is the Alberta Stroke Program Early CT Score (ASPECTS), which was used for scoring of neuroimaging results in this work. ASPECTS is

based on the evaluation of the topography of the brain lesion [37]. The territory of the MCA is divided into 10 regions of interest (M1-M6, I = insula, IC = internal capsule, L = lenticular, and C = caudate) and the different areas of the MCA territory are then weighted on the basis of functional importance rather than extent of injury [37]. A score of 10, maximum score, is compatible with absence of visible injury in the ACM territory [37]. ASPECTS can be used as an instrument to evaluate the risk of hemorrhagic transformation after fibrinolysis, and as a potential predictor of functional recovery [37].

Transcranial Doppler Ultrasound (TD) is a complementary imaging technique with great interest and potential, given that is a non-invasive, financially sustainable, portable and secure method, which allows the evaluation of intracerebral blood flow. In MCA occlusions, TD shows high sensitivity, specificity and positive predictive value when compared with angiography. TD is a relevant tool to detect intracranial vascular occlusions, as well as monitoring thrombolytic treatment by assessing the existence of cerebral recanalization [10].

Conventional cerebral angiography is of all exams the one providing most specific and sensitive image, allowing the visualization of acute MCA occlusions in the first six hours, as well as the existence of recanalization of the blood flow. Angiography allows excellent visualization of vessel anatomy. location, extent and degree of stenosis, as well as the existence of collateral circulation. However, its recent exponential growth is related to its therapeutic application. In fact, endovascular treatment for acute occlusions of a large intracranial vessel is already recommended by all international scientific societies. Angiography is, still, an invasive technique, and as such is not used for screening purposes [8, 9].

Diffusion-weighted magnetic resonance imaging (DW-MRI) represents an important technological advance in the overall field of neuroimaging, since it allows noninvasive examination of the diffusion of water molecules in brain tissue. It is mainly indicated for the evaluation and diagnosis of acute brain lesions in symptomatic patients where T2-weighted magnetic resonance imaging (MRI)/ FLAIR (fluid-attenuated inversion recovery) do not show alterations. It has a rate of detection of ischemic lesions higher than 95% and its high precision to identify irreversible tissue damage in the first hours of acute lesion has been demonstrated. The clinical component (duration of symptoms, changes in communication capacity, motor capacity and etiology) seems to be directly correlated with the degree of brain tissue damage identified in DW-MRI. Thus, DW-MRI provides clinically useful information for diagnosis, etiology, therapeutic decision-making, prevention, follow-up, and functional prognosis of patients after acute brain injury [36]. On the other hand, brain changes found in conventional MRI in patients with brain injury do not present robust long-term predictive value in terms of functional prognosis post-stroke [38].

Treatment: fibrinolysis/thrombectomy

Recanalization of injured brain tissue (ischemic penumbra) is considered an important predictor of clinical and functional recovery in stroke patients [39, 40]. Cell viability is maintained for a few hours, and, thus, function can potentially be maintained if blood flow is restored in a timely manner [41, 42]. Recanalization can occur spontaneously in 17% to 67% of ischemic strokes within 48 hours with clinical implications in terms of prognosis [43]. Furthermore, in 86% of cases, spontaneous

recanalization can eventually occur up to two weeks after stroke, but at this point no longer having any clinical or functional impact [40].

Over the past 30 years, important advances have been made in the development of recanalization techniques, such as endovenous thrombolysis (chemistry) with recombinant tissue plasminogen activator (rt-PA) and endovascular (mechanical) thrombectomy [8, 40, 42]. Intravenous thrombolysis with rt-PA when administered within the first 4.5 hours after symptom onset reduces the probability of adverse prognosis by 7%, with clinical results at 90 days [8, 44–46] and functional results at 3 and 6 months [45, 47, 48]. The technique affects recanalization rates in 13 to 50% of large vessel occlusions [45]. The main limitations are the narrow temporal window in which it can be applied, the incomplete recanalization of large thrombi, and the potential risk of hemorrhagic transformation [45].

Minimally invasive endovascular techniques have also been developed over the last few decades. These use of intra-arterial devices to mechanically remove thrombi and be used up to 24 hours after symptom onset in patients with contraindications or no benefit following endovascular thrombolysis, with recanalization rates of up to 54% [46, 47, 49]. The most frequent complications are vascular perforation, intramural excretion and embolization of a previously unaffected vascular territory [45, 47, 50]. Several studies have demonstrated the superiority of combined treatment—i.e. mechanical thrombectomy and rt-PA—in large vessel occlusions within the first 4.5 hours after symptom onset [45].

The selection of patients for recanalization techniques is based on clinical and temporal criteria, as well as the absence of contraindications [8, 9, 51]. Improving these criteria would increase the likelihood of successful recanalization. In this context, the role of several biomarkers as diagnostic, prognostic, and therapeutic decision support tools has recently been discussed. The biomarker S100 calcium binding protein β (S100β), a calcium binding protein in the neuronal system, is an indicator of neurological toxicity [25, 52] and can be potentially applied in diagnosis and prognosis, since it is associated with stroke severity, stroke volume, and hemorrhagic transformation [53–58].

Biomarkers

There has been and increasing interest in the identification and validation of biomarkers in medicine overall, and specifically in the management of stroke patients, as illustrated in Figure 1.7.

A biomarker is a molecule that can be measured in the peripheral blood, cerebrospinal fluid (CSF) or a tissue component. For the ideal biomarker, measurement should be effective, specific and sensitive to the pathology being studied.

Markers of inflammation, hemostasis, altered cardiac and neurological function, can help in establishing accurate prognosis in stroke patients, as well as screening of patients that could benefit from specific treatment.

The most commonly studied stroke biomarkers are the S100β, neuronspecific enolase (NSE), myelin basic protein (MBP) and glial fibrillary acidic protein (GFAP). The main challenges in using such biomarkers in the context of stroke are the lack of specificity, the permeability of the blood-brain barrier and the determination in the peripheral blood.

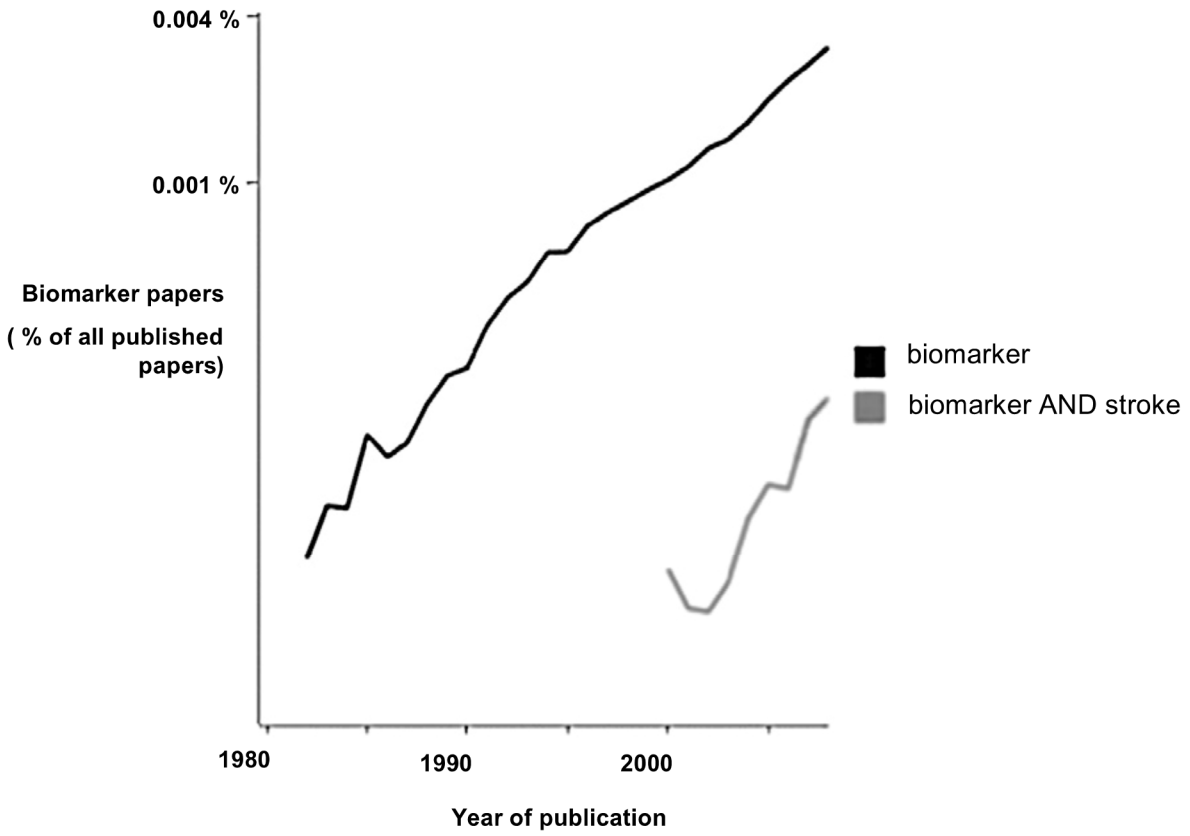

Figure 1.7 – Evolution of publications with the terms 'biomarker' or 'biomarkers' and 'stroke' in Medline.

Data are shown on a logarithmic scale. Adapted with permission from: Whiteley W, Tian Y, Jickling GC. Int J Stroke. 2012;7(5):435-439.

Several proteins involved in inflammation and immune response have also been identified as stroke biomarkers, including C-reactive protein (CRP), interleukin-6 (IL-6), Tumor Necrosis Factor α (TNF-α), Vascular cell adhesion protein 1 (VCAM 1), intercellular adhesion molecule 1 (ICAM 1), N-methyl-d-aspartate (NMDA) receptor antibodies, and matrix metalloproteinases (MMPs). Likewise, the molecules involved in acute hemostasis have also been associated with ischemic stroke, including fibrinogen, D-dimer and von Willebrand factor (vWF).

S100β protein is found at high concentrations in glial and Schwann cells. Several studies report that S100β increases significantly in peripheral blood as well as in CSF after brain injury and neurodegenerative diseases. The increase of S100β in the serum of patients with stroke begins as early as within 12 hours, with a peak between 2–3 days post-injury [5, 6], with a half-life of 2 hours [7].

According to recent studies, blood biomarkers can provide useful information in predicting the prognosis in the acute phase after stroke. Although some markers have predictive capacity, none of the studies was able to demonstrate the value of these biomarkers in the validation of a potential clinical model.

In chapter 4, the use of the various biomarkers as potential predictors of functional prognosis after stroke is further explored.

Prognosis

Traditionally, studies on stroke were focused on the relatively short-term vital prognosis after the acute episode. However, given the increases in life expectancy and need to improve patient quality of life (QoL), functional prognosis has started to be seen as a main treatment goal in these patients with growing interest among clinicians and researchers.

After an episode of acute stroke, the clinician is often asked about the long-term prognosis and the potential for functional recovery. Several factors are currently known to influence prognosis including: age, mechanism, location and severity of the lesion, previous comorbidities, clinical findings, and related complications. Knowledge of these factors is crucial for prognostic prediction, but it is also important for defining the clinical approach and for informing the patient and family about the course of the disease.

Since the mechanisms of injury underlying ischemic and hemorrhagic stroke are distinct, recovery time and outcome are also expected to be different. From the perspective of PRM, the insights from the pathophysiology mechanisms as well as the patient-associated factors that could influence prognosis are important to establish the most effective rehabilitation approach, which makes sure patients reach their full potential.

Ischemic stroke

In patients who do not have other complications, moderate recovery of neurological deficits might occur within 12 hours to 7 days after ischemic stroke [59]. The vast majority of post-event recovery occurs within the first 3 to 6 months [60, 61], and in some patients this period may extend up to 18 months [61]. In a prospective study involving more than 1000 patients with ischemic stroke, the group with mild disability recovered within approximately 2 months, the group with moderate disability approximately 3 months, the group recovering from severe disability within 4 months, and those who had the greatest disability levels recovered in 5 months [62, 63]. Motor recovery appears to require integrity of the ipsilesional corticospinal tract, and injury at this level is a predictor of worse prognosis [64–66]. Functional outcome achieved at 3 months after acute stroke has also been found to predict 4-year survival [67], and 6-month functional status to predict long-term survival [68].

In terms of specific neurological deficits, prognostic prediction is more challenging. Nevertheless, with a clinical evaluation and careful review of images carried out by an experienced physician, it is possible to predict with some degree of safety the potential for functional recovery. The timing and degree of improvement varies from deficit to deficit, although, as a general rule, the lighter the deficit, the faster the recovery can be [60].

Upper limb (upper limb function)

Functional gains of the upper limb and hand are particularly important for overall functional recovery. Several studies report that active finger extension movements, claw release, abduction of the shoulder and presence of active range of motion are associated with a more favorable prognosis for recovery at 6 months [69–71]. In a prospective cohort study with 188 patients with monoparesis or

hemiparesis sequelae following ischemic stroke in the territory of the anterior circulation, those who had some voluntary movement of finger extension and abduction of the hemiplegic shoulder at day 2 were more likely to recover their prowess at 6 months [72]. On the other hand, the probability of recovery of patients without these voluntary movements at 2 to 9 days after the acute event is 0.25 and 0.14, respectively. One study reports that in patients with hemiplegia, the first voluntary movements were observed at 6 to 33 days post-event [73]. In another prospective study, maximum functional recovery was achieved at 3 weeks post-event by 80% of patients and at 9 weeks by 95% of patients [74]. Complete functional recovery of the upper limb was observed in patients with mild and severe initial paresis of 79 and 18%, respectively.

Lower limb and gait (lower limb function)

In a study with 154 patients who were unable to walk after ischemic stroke, a multivariate model showed that patients who were able to balance in sitting for 30 seconds and were able to do muscle contraction (with or without effective movement) on the paretic side in the first 72 hours after the event had a probability of recovery of gait at 6 months of 98% [75]. In those patients who did not experience such movements at 72 hours after the event, the probability of autonomous gait recovery was only 27%.

Language impairment (aphasia)

Patients with aphasia are likely to experience some improvement. The prognosis of total recovery is greater the milder the initial aphasia. A prospective study involving 300 patients with initial aphasia showed that time to maximum recovery in 95% of patients with mild, moderate, and severe aphasia was 2, 6, and 10 weeks respectively [76].

Swallowing impairment (dysphagia)

Approximately 50% of patients have dysphagia after ischemic stroke [77], which often improves over time. A multicenter study found no benefit in early enteral feeding via percutaneous endoscopic gastrostomy (PEG) compared to having no tube [78]. Some risk factors that lead to a lengthier recovery with later need for PEG placement include high NIHSS score, and bi-hemispheric involvement [79, 80]. In a retrospective cohort study of 563 hospitalized patients for post-stroke rehabilitation, feeding tubes were placed in 6% [81]. Of these, approximately one third were removed before discharge, and almost all others were removed within 1 year. Patients with bilateral or posterior ischemic lesions were less likely to return to oral feeding.

Sensitivity impairment

Sensitivity compromise is observed in 65-94% of ischemic stroke patients [82], which leads to reduced mobility and independence in ADLs [83]. Currently, there are no predictors in the literature that accurately indicate what the recovery of sensitivity will be like. Stroke with involvement of the spinothalamic or trigeminal band sometimes develop a debilitating central pain syndrome [84].

Visual impairment

Regarding visual impairments, evidence is still limited in the literature, but suggests complete recovery in 70–80% of patients at 3 months after ischemic stroke [85, 86]. A study of 99 patients with post-stroke homonymous hemianopsia (HH) showed that 17% of those with complete HH had recovery of the deficits at 1 month, while 72% of those with partial HH achieved full recovery [87].

Hemorrhagic stroke

Intracerebral hemorrhage (primary or secondary) accounts for about 20% of all strokes and is associated with a higher acute-phase mortality rate (40–50%) when compared to ischemic events [88]. However, it is also generally recognized hemorrhagic stroke lead to better prognosis in terms of neurological and functional recovery [88], but there is still a need to validate this general understanding with appropriate evidence.

The severity of hemorrhagic stroke is considered the factor with the greatest impact on prognosis, since the resulting disability is a consequence of the underlying neurological deficits. A prospective study of 160 patients, which compared the patterns in head CT, found that the best survival outcome was associated with localized hemorrhage in the basal ganglia/internal capsule regions (86.7%), followed by lobar hemorrhage [89]. The best functional outcome was associated with hematomas with volume <30mL [89].

A longitudinal study of 274 patients (229 ischemic and 45 hemorrhagic), assessed the Barthel score at admission, 8, 10, 12, 26, and 52 weeks post-stroke. In terms of ADLs, recovery did not follow a linear pattern, but there were significant gains up to week 26 in ischemic stroke and up to week 10 in hemorrhagic stroke [90]. A cohort study with 2076 patients suggests that long-term general recovery of the group of patients with subarachnoid hemorrhage was better than that of the intracerebral hemorrhage group. Patients who initially presented moderate to severe subarachnoid hemorrhage had a good recovery at 12 months post-stroke [91].

A longitudinal observational study with 11 patients showed that trunk balance, lower limb motor function and sensory deficits improved significantly in the first 3 months after injury, after which the improvements were not significant. Upper limb function and gait did not change in the first month but improved significantly from 3 to 6 months after the event (mainly gait). The involvement of the anterior putamen, internal capsule, thalamus, periventricular white matter and pre-motor cortex was related to precarious recovery of the upper limb [92].

And additional prospective study of 20 patients with 6 months of follow-up evaluated upper and lower limb motor function, gait capacity, trunk balance, sensitivity and cognition at various timepoints: hospital admission, 1, 2, and 4 weeks and at 3, 4, 5 and 6 months post-hemorrhagic stroke [93]. The fastest recovery occurred in the first 4 weeks of rehabilitation, decelerating between 3 and 6 months after injury. Functional recovery in the lower limb was faster relative to the upper limb. All parameters (except lower limb function) continued to improve up to 6 months post-stroke.

Rehabilitation program

Recovery, re-adaptation and rehabilitation

Implementing an effective rehabilitation program requires the participation of a multiprofessional team, consisting of a physiatrist, nurse, physiotherapist, occupational therapist, speech therapist, psychologist/neuropsychologist, and social worker not forgetting the patient and family/caregiver, the core of the "Rehabilitation Team" [94].

The rehabilitation program aims at acquiring maximum functional capacity and autonomy, either through the recovery of previous capacities or through re-adaptation mechanisms. The fundamental principle is to facilitate/accelerate the mechanisms of neuroplasticity—promoting recovery first, while re-adaptation is reserved for when the maximum recovery threshold is reached [94]. Rehabilitation should be started as early as possible (in a clinically stable patient) and should establish specific goals with increasing/ challenging degrees of difficulty for the patient [95, 96].

Accumulating evidence suggests the existence of a critical window for recovery after stroke of approximately 12 weeks, as a result of increased neuroplasticity in the short-term after an acute stroke episode (Figure 1.8). This very short window provides compelling evidence for using the highest possible doses and intensity of neurorehabilitation in the first weeks and months after acute stroke.

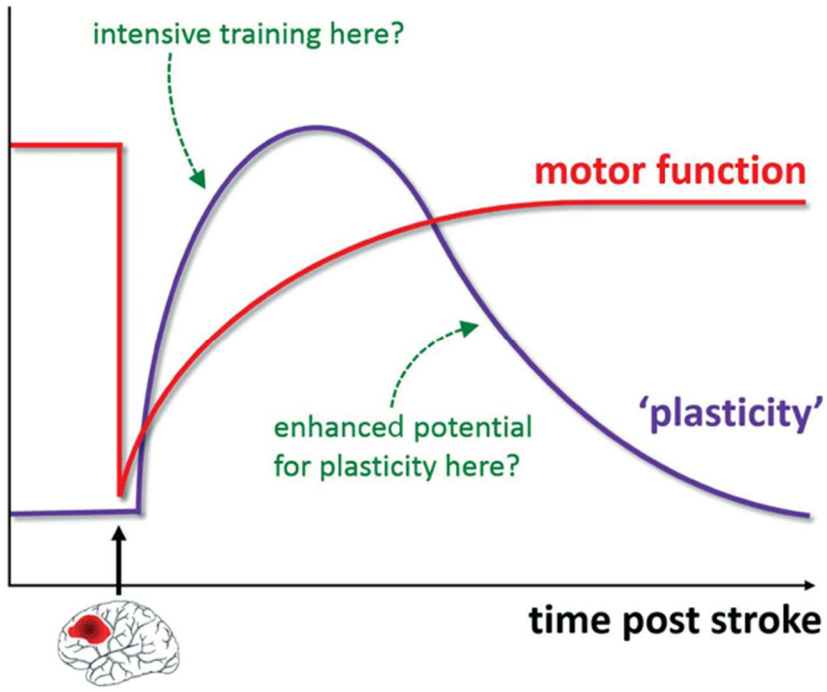

Figure 1.8 – Impact of neuroplasticity in motor function outcomes after stroke.
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Sensitive and motor control

Hemiplegia is the most frequent motor sequela (88%) after stroke [94]. Maximum functional recovery occurs, on average, around 3 to 6 months, although a degree of minor recovery might still occur after this period [32, 33].

In the initial stages, development of contractures and peripheral neuropathies should be prevented, through correct positioning, caution with transfers, passive/active-assisted polissegmental mobilizations, and stretching (if there are muscle tone alterations) [33]. After the acute phase, several techniques can be used to promote motor rehabilitation, and these should be used concomitantly. None of the techniques present evidence of superiority and, thus, they should not be employed in isolation as the single rehabilitation approach [95].

The traditional therapy consists in the application of positioning techniques, passive/active joint mobilization exercises, stretching, compensatory techniques and muscular resistance training, emphasizing the need for repetition of specific movements [32]. In this context, the practice of physical exercise with therapeutic purposes—including aerobic training, muscle strengthening and flexibility—seems to play an important role in patient recovery [97].

The proprioceptive neuromuscular facilitation is based on spiral and diagonal movements in order to facilitate synergic patterns of movement with functional basis [32]. Neurodevelopment techniques, such as the Bobath technique, have as their main objective the inhibition of primitive patterns [32]. Movement therapy techniques, such as the Brunnstrom technique, use primitive synergistic patterns in an attempt to improve motor control through central facilitation [32].

These techniques can be complemented by others: sensory stimulation, mental practice techniques (through the imagination of the intended movement), therapy with mirrors, techniques of induced movement by restricting the unaffected limb and strategies aided by robotics and virtual reality scenarios [33, 96, 97]. The use of virtual environments is increasing, and this appears to be stimulant and well-accepted by patients, however, their efficacy appears to be only slightly better than traditional therapies [98]. Thus, since these require expensive equipment, their use is recommended only as an adjunct to traditional therapies [98]. Functional electrical stimulation, non-invasive brain stimulation and transcranial magnetic stimulation have also shown some evidence of benefit, although current evidence is still not sufficiently robust [33].

Several studies have argued that pharmacological interventions may play an important role in motor recovery and improvements in communication [97, 99]. Amphetamines, dopaminergics and selective serotonin reuptake inhibitors are the most tested agents, although their use is still not supported by strong evidence [99]. The use of orthoses should be judicious and reserved to assist in positioning (maintain/increase joint range amplitude in passive movement), facilitate function or increase comfort [94].

Gait

Hemiparetic gait is characterized by asymmetry associated with the extensor synergetic pattern of the lower limb—hip in extension and adduction, knee in extension, and ankle in plantar flexion and

inversion [100]. These changes increase the energy required for locomotion and call into question patient safety [100].

All patients should initiate gait training as early as possible [94]. The initial objectives are to achieve good static and dynamic balance of the trunk and pelvic girdle, acquisition and maintenance of orthostatism, ability to perform transfers, and ability to go up/down stairs [33].

In the initial stages, treadmill training with partial load suspension seems to be of benefit [33]. Where appropriate, different walking aids should be used. Ankle-foot orthotics are widely used in these patients, since they facilitate the detachment capacity of the foot at the beginning of the oscillating phase and confer stability to the joint in the loading phase [94].

Spasticity

Spasticity is the resistance experienced when performing a passive stretching movement of a given muscle, being speed-dependent [33]. This change is common in lesions of the 1st neuron, as a result of hyperexcitability of the monosynaptic pathways, due to changes in supraspinal inhibitory pathways [33]. These changes result in stereotyped postures, usually occurring days to weeks after acute stroke [101]. Spasticity may have an important functional impact, conditioning changes in resting posture, gait execution or response to stimuli [32, 33]. The spastic pattern is classically characterized by flexor synergies of the upper limbs and extensor synergies of the lower limbs [33]. The most widely used instrument for the evaluation of spasticity is the Modified Ashworth Scale [33].

Treatment encompasses (a) a non-pharmacological approach, through antispastic techniques: stretching, positioning (which may involve the use of orthoses), physical agents (ultrasound and thermotherapy); (b) a pharmacological approach with oral antispasmodic agents (baclofen and tizanidine) or invasive techniques (intramuscular injection of botulinum toxin, phenol blockade, implantation of intrathecal baclofen pump); and (c) surgical procedures as a last resort [33, 101].

Upper limb rehabilitation program

The rehabilitation of the upper limb poses substantial challenges for clinicians and the multiprofessional team, since it shows substantial differences compared to the lower limb. Such challenges highlight the need for substantial further research into upper limb rehabilitation.

Among the various neurological disorders that emerge after a stroke, hemiparesis of brachial predominance is a common and undesirable consequence. This issue affects approximately 85% of stroke patients [33], with 55–75% reporting deficits in upper limb function that compromise their daily life and work activities. Therefore, this clinical condition makes upper limb recovery an important and challenging goal for clinicians and healthcare professionals.

Several recent studies assessed upper limb rehabilitation in stroke patients. New techniques, still under evaluation, are becoming the practical applications of the concept of post-stroke brain plasticity.

Of note, motor strength tends to recover initially in the proximal extremity before progressing distally, although recent studies suggest proximal and distal function may be equally impaired [102]. The pattern of recovery after MCA stroke tends towards earlier and fuller improvement of the leg compared to the arm. The Copenhagen Stroke Study, which assessed multiple outcomes via a

population-based analysis, concluded that most upper limb functional recovery can be expected within 6 to 11 weeks after stroke [103]. A significant number of patients in this cohort had poorly functioning upper limbs, despite intensive rehabilitation, with improvements noted only if there was compensation by the unaffected limb.

Brogardh et al. demonstrated expanded and contracted areas in the M1 region that correlated to digital training tasks in normal intact primates [104]. Similar findings by Kleim demonstrated increased cortical representation in rodent motor cortices of the wrist and digit, and decreases in the elbow and shoulder regions ten days after training on a skilled reaching task [105]. Animal models also show similar cortical reorganization after brain injury.

Monkey brains mapped 12 weeks after stroke in the primary motor cortex for the hand demonstrated increased representation of the hand in the premotor cortex indicating “injury-induced” plasticity. In other words, neural reorganization occurred in other sites in response to cortical damage. The degree of expansion corresponded to the degree of injury in the primary motor cortex [106]. Another study using neuroanatomical tracers demonstrated axonal sprouting near the area of injury in monkey brains as well as in more remote areas [107].

Repetitive task training is a mainstay of standard therapy and is defined as repeated practice of tasks that are functional in nature, in contrast to basic muscle strengthening. However, a Cochrane review in 2007 demonstrated that while this approach is useful for improvement in lower limb function, there is little direct advantage for upper limb function [108]. In chronic spastic hemiparesis, there is evidence that task practice combined with onabotulininumtoxinA injections is effective in improving upper limb motor function [109].

Hand rehabilitation

Most strategies described in the literature are based on the activation of the ipsilateral motor cortex, inhibition of the contralesional motor cortex and/or modulation of the sensitive afferents.

The classic rehabilitation program comprises physical therapy and occupational therapy. It is estimated that 25 hours of exercise lead to greater benefit compared to the classic 10-hour acute phase program (functional rehabilitation in case of moderate impairment, classic program in severe impairment). Sensorimotor training with "Arm BASIS training" is dedicated to patients with severe sequelae, presenting only improvements in motor scores. Sensory transcutaneous electrical nerve stimulation (SENS) prior to the session may enhance motor training through ipslateral intracortical inhibition [110]. Thermal stimulation may promote the recovery of proximal motricity in the acute/subacute phase [111]. Electroacupuncture enhances functional improvement in the acute phase [112].

Bimanual coordination is often compromised in stroke [113, 114]. However, bimanual training does not seem to be clearly superior or as effective as unilateral tasks [115–119].

Mirror therapy [120–122] (30 min/day for 4 weeks) showed improved autonomy and motor capacity for up to 6 months. If the lesion is in the DH, response to mirror therapy may be ever better [123].

Feedback is useful in the reorganization of the sensory-motor brain map regarding the distal representation of the affected arm. Subacute cases with severe compromise may benefit from a transient regional anesthesia of the upper brachial plexus roots, showing improvements in motor and functional performance in the paretic hand [124, 125], when the proximal synchysis pattern still plays a minimal role in conditioning distal motricity.

Constrained induced movement therapy is an intensive therapy (60 hours, 6h/day, over a period of more than 10 days) where functional tasks are performed in parts, repeatedly, with increasing complexity over time. It requires motivation, preserved cognition, risk of minor fall and minimal distal motor capacity, including 10º of active extension of fingers and 20º of the fist. In the acute phase of stroke (starting before the 10-15th day after event) it presents significant functional benefit [126–128]. In the chronic phase, the use of the limb in terms of quality and frequency in the activities of daily living (ADL) improved [129], with less evident results in terms of execution speed.

Mental image is a conscious representation based on the subliminal activation of the neuromotor system, requiring cognitive integrity [130]. In the chronic phase of stroke, after rehabilitation exercises, mental image techniques considerably improve motor and functional capacity of the arm [131]. In the subacute phase and/or with severe affection, there is little evidence of its impact.

High frequency transcranial magnetic stimulation (TMS) may, in patients with chronic stroke and mild motor impairment, lead to greater accuracy and speed of distal motor execution immediately after the session, which suggests a motor facilitation phenomenon. Transcranial electrical stimulation of the ipsilesional motor cortex is proposed for functional improvement of the arm in chronic stroke and moderate motor compromise (> 2 years), with results comparable to those obtained by repetitive transcranial magnetic stimulation (rTMS) [132]. A single session of low frequency TMS in the healthy motor cortex (7 days post-stroke) showed immediate improvement of manual dexterity but not palmar pinch strength [133]. Also, rTMS in patients with chronic stroke seems to improve the grip speed between thumb and 1st finger, but not strength [134]. Repetitive sessions in the healthy hemisphere in chronic left subcortical stroke (1 year) showed a correlation between manual function and changes in the excitability of the injured cortex, thus showing a lengthier and lasting effect and validating the safety of this method [135].

Neuromuscular electrostimulation can be used in the acute or chronic phase of stroke, regardless of the degree of motor compromise. The choice of parameters remains empirical, however, and requires validation. Motor and manual dexterity gains in patients with chronic stroke with moderate sequelae appear to be superior under distal electromyography-triggered neuromuscular stimulation (EMG-stim) versus functional electrical stimulation (FES) [109, 136]. The combination of EMG-stim and bilateral distal training proved to be beneficial in patients with chronic stroke and moderate disability. On the contrary, proximal FES seems to have an insufficient efficacy at the end of 3 months [137], since the proximal reinforcement during acute rehabilitation impairs the cortical representation of the distal muscles, limiting hand recovery. Distal electrostimulation is an integral part of the functional strategy, since it can facilitate hand opening and thus optimizing rehabilitation [138, 139]. Nonetheless, these results require further validation.

The combination of botulinum toxin type A, EMG-stim, and restrictive therapy should be studied, since the forced inactivity of spastic muscles complements the reinforcement of useful affected muscles [140–142].

Virtual reality offers greater sensory feedback, but it requires motivation on the part of the patient. 2D training (1h/day for 4 weeks) showed improved function in chronic stroke [143].

Robotic therapy can provide great sensorimotor support, with the advantage of having multiple modalities for voluntary motor facilitation (passive, active-assisted, active, adjusted counter-resistance, uni or bimanual). Sensory feedback is allowed by an external device. Robotic therapy can reduce the time in which therapist is required and, therefore, also reduce hospitalization times. In the acute phase of stroke, the NeReBot (unimanual) allows repetitive basic movements of the shoulder and elbow, eliminating gravity. Early use leads to functional improvement of the hand [144]. In acute stroke, the BiManuTrack robot (bimanual) also improves the voluntary motor capacity of the wrist in patients with severe compromise. The treatment consists of 20min/day, 5 days/week, for 6 weeks [145]. In chronic severe stroke, the Mirror image movement enabler (MIME) can be used, which allows symmetrical bilateral movement with better results than neurodevelopment [146], although with no motor differences. The BATRAC ("Bilateral Arm Training With Rhythmic Auditory Cueing") is similar to MIME but allows to alternate in-phase and anti-phase movements [147]. It is more specific for training of motor skills. In all degrees of compromise, neurodevelopmental therapies have been showing less promising results.

PART B

RESEARCH PLAN

CHAPTER 2

AIMS

Aims and hypotheses

The prognosis of patients with stroke is highly relevant for both clinicians and researchers. Over decades, the identification of neural lesions and biomarkers, specifically in the central nervous system, has been challenging as well as a source of controversy due to the limitation of available studies. Therefore, there is a clear need to further develop predictive models in this context, especially in what concerns functional prognosis (instead of only studying vital prognosis). The reliability of current models would probably improve by identifying accurate blood markers of pathological processes involved in acute ischemic stroke (inflammation, hemostasis, neuronal or glial damage), examining demographic factors, developing and validating reliable metric instruments for the acute phase, using the most sensitive and specific imaging exams and scoring systems.

This work will focus on upper limb recovery since this is one of the most important aspects driving disability after stroke. After stroke there is a relatively well-established window of neuroplasticity of 12 weeks and, therefore, intervention should be primarily targeted within this short timeframe. With this work we will try to address the current need to better understand the prognostic factors for patient functioning after stroke. Although some biomarkers and neuroimaging techniques show promising predictive capacity, none of the studies evaluating these methodologies alone or in association is capable of sustaining the validation of a potential model for clinical prognosis of functioning. Thus, current evidence remains insufficient to determine with precision the functional outcome in the first hours after the stroke, which would be highly valuable for tailoring rehabilitation programs. Hence, we aim to produce evidence capable of contributing to the accurate prediction of patient functioning after stroke, with applicable clinical value in the acute phase.

This work aims to determine the predictive value of various demographic/clinical factors, biomarkers, and imaging techniques for short- and medium-term functional prognosis in patients with acute stroke. These data will provide valuable insight in developing an instrument which can be applied in clinical practice as an early predictor of functional prognosis in acute stroke patients. Ultimately, the formulation of an objective, reproducible, sensitive, and feasible clinical model will allow early screening of patients for tailored rehabilitation programs, controlling resources and ultimately leading to better functioning.

Hypothesis

- Biomarker levels, including CPR, D-Dimer, and fibrinogen at hospital admission, and S100β levels in peripheral blood at 48 hours post-stroke are associated with acute stroke severity and predict functional outcome at 12 weeks.
- Patients with worse clinical condition at hospital admission (measured through NIHSS) and with worse upper limb function at 48 hours (measured through SULCS) will present worse functional outcomes at 12 and 24 weeks after stroke.
- The most relevant functional gains occur within the first 12 weeks after the acute event, which provides an important window of action for patient recovery.

- Recanalization, either spontaneous or therapeutic, in the first 24 hours post-stroke reduces the volume of brain lesion and, consequently, patients have better functional prognosis (both in terms of general functioning and, specifically, upper limb functioning).
- The evaluation of several demographic factors, imaging of the brain lesion (head CT with ASPECTS scoring) and determination of blood biomarkers up to 48 hours after stroke, allow the formulation of a clinical model to predict functional prognosis of the upper limb in stroke patients at 12 weeks after the acute event.

CHAPTER 3

OVERALL METHODOLOGY

Study design

We worked essentially with two cohorts of patients. One cohort was used to validate the SULCS assessment scale for the Portuguese population. This validation study is described in detail in Chapter 5. The other cohort consisted of ischemic stroke patients in which all the remaining evaluations were conducted. The characteristics of this cohort and the overall study methodology employed are described below. Patients were included in the study after hospital admission in the Stroke Unit of Centro Hospitalar e Universitário de Coimbra; when stable from a hemodynamic standpoint, patients were admitted to Centro de Medicina de Reabilitação da Região Centro Rovisco Pais where they followed a rehabilitation program according to routine clinical practice. The collaboration between these two entities was approved by both administrations specifically for the purposes of this study.

Selection criteria

All patients with age 18–85 years and clinical and radiological evaluation indicative of ischemic stroke in the territory of the MCA (confirmed through head CT) were eligible to participate. The recruitment period lasted from April 2015 to April 2016. Patients were excluded from the study if symptom onset occurred more than 3 hours prior to hospital admission, if there were signs of hemorrhagic transformation, if the they showed pre-morbid disability (mRS>2), and if there were other neurological, inflammatory, or neoplastic conditions. Patients with cognitive or behavioral impairments that would not allow continued participation in the study were also excluded. Figure 3.1 summarizes the patient recruitment process for these studies.

Clinical and laboratory evaluation

All patients were observed by a vascular neurologist on study inclusion, corresponding to a maximum period of 6 hours after symptom onset (only patients that presented to the ER within 3 hours of symptom onset were included as mentioned above). Peripheral blood was collected (prior to any fibrinolytic/thrombolytic therapy was introduced) for measurement of biomarkers of interest (CRP, D-Dimer, and fibrinogen). Blood was sent for analysis, with no associated clinical information (i.e. blind sample). At this timepoint, demographic and clinical data were collected, including age, gender, stroke etiology according to TOAST classification [18], stroke severity according to the National Institutes of Health Stroke Scale (NIHSS), and the presence of vascular risk factors, namely hypertension, diabetes mellitus (DM), dyslipidemia, smoking history, hyperuricemia, obesity, atrial fibrillation (AF), and heart failure (HF).

At 48 hours after admission, a new sample of peripheral blood was sent to the laboratory with no associated clinical information for S100β protein assay.

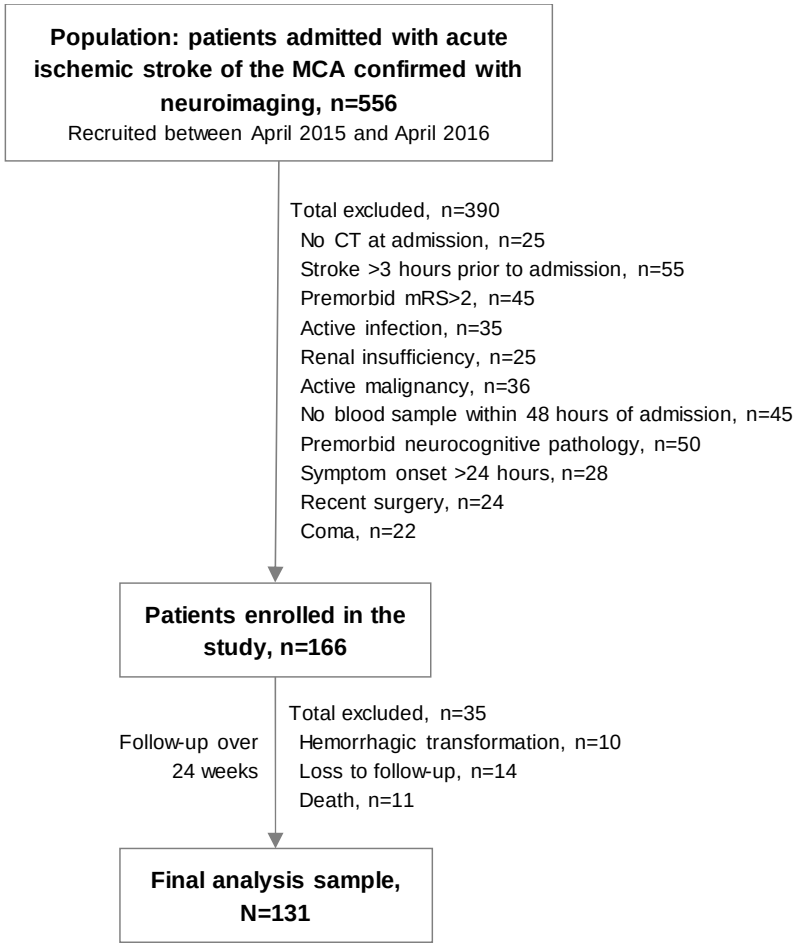

Figure 3.1 – Summary of the patient recruitment process.

Outcome assessments

Patients were observed in several stages: at admission to the ER, 24 hours, 48 hours and 3, 12, and 24 weeks after stroke. At each stage, different clinical, laboratory, and functional assessments (NIHSS, SULCS, mRS and FIM) were performed, as presented in the assessment schedule shown in Table 3.1.

Assessment scales

SULCS is a unidimensional, hierarchical scale specifically designed to evaluate upper limb functioning in stroke patients. It is based on the execution of 10 tasks of increasing difficulty. The score corresponds to the number of tasks the patient is able to execute. Scores 0–3 indicate no hand function, scores 4–7 indicate basic hand function, and scores 8–10 indicate good hand function. The recently published Portuguese version of SULCS was used in this study.

mRS is a widely used assessment scale that evaluates the degree of disability and dependency in activities of daily living. The scale is divided into 7 degrees of ascending disability, in which 0

corresponds to patients with no visible symptoms of disability and 6 corresponds to death. In this study, the Portuguese validated version of mRS was used.

Table 3.1 – Assessment schedule over the study period.

Assessment	Admission	24h	48h	3 Weeks	12 Weeks	24 Weeks
Demographics	×					
Clinical characteristics	×					
NIHSS	×					
CRP	×					
D-Dimer	×					
Fibrinogen	×					
ASPECTS		×				
S100B			×			
SULCS			×	×	×	×
mRS			×	×	×	×
FIM			×	×	×	×

ASPECTS: Alberta Stroke Program Early CT Score; CRP: C-reactive protein; FIM:Functional independence scale; mRS: Modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; S100β: S100 calcium binding protein β; SULCS: Stroke Upper Limb Capacity Scale

FIM allows the measurement of disability in both physical and cognitive dimensions. The scale consists of 18 items scored 1 to 7, in which higher scores indicate higher degree of functioning and independence in executing ADLs. The items fall into 2 domains: (1) motor domain (M-FIM), which evaluates self-care, sphincter control, transfers, and locomotion, and (2) cognitive domain (C-FIM), which evaluates communication and social cognition. The Portuguese translation of FIM currently recommended by the National Health General Directorate was used.

ASPECTS is aimed at providing a quantitative measure of brain lesion, based on topographic analyses. It is obtained by dividing the territory of the middle cerebral artery into 10 regions of interest (M1-M6, I = Insular ribbon, IC = Internal capsule, L = Lenticular nucleus, and C = Caudate nucleus). The areas of the middle cerebral artery are considered based on their functional relevance instead of brain lesion extension. To calculate the final score, 1 point is subtracted from 10 for each of the regions of interest that show signs of brain lesion, thus lower scores are indicative of more extensive brain lesions. This score is fundamentally used in the consideration of recanalization therapies in the acute setting; however, it has also been used to quantify the extension of cerebral damage in subacute neuroimaging exams. In our project we used the ASPECTS graded by a neuroradiologist in the 24 hours CT as a measure of subacute lesion.

All these scales were applied by the principal investigator (where aplicable).

Treatment and rehabilitation

During the period of the study, patients received treatment according to routine clinical practice and underwent a closely controlled rehabilitation program, following current clinical practice in the study center. In the first 12 weeks participants received inpatient care at the study center, which included

60 minutes of physical therapy, 30 minutes of occupational therapy, and 30 minutes of speech therapy (if aphasia was present) daily, 5 days per week [93, 148]. Patients who achieved maximum scores for all assessment scales and did not need further medical care, were discharged and then reevaluated at 12 weeks. The remaining patients continued the rehabilitation program in ambulatory setting in the area of residency until week 24, in strict collaboration with the attending primary care physician. After discharge, patients were instructed to continue the daily rehabilitation program at home, including 60 minutes of physical therapy, 30 minutes of occupational therapy, and 30 minutes of speech therapy (if aphasia was present) daily, 5 days per week. The study team made all reasonable efforts to ensure patients complied with the rehabilitation program.

Neurological rehabilitation exercises included balance-coordination training, hand rehabilitation, stretching and relaxation exercises, walking exercises, and posture exercises. Exercises focused mainly on using the affected limb, symmetric weight bearing and transfer, mat activities, and gait training [93, 148].

Ethical review

The study was evaluated and approved by the Scientific Council of the Ethics Committee of the Faculty of Medicine of the University of Coimbra (reference letter 104-CE-2014).

Informed consent and data protection

Patients or their legal representatives provided their written informed consent prior to enrolment in the study. Only the minimal required patient data were used in the study database, without patient identification. All patient data were treated confidentially and following best practices for data protection in clinical research.

Statistical analysis

Quantitative variables were presented as mean and standard deviation if normality of distribution was confirmed through the Shapiro-Wilk test or otherwise presented as median plus 25^{th}, 75^{th} percentiles. Categorical variables were presented as absolute and relative frequencies.

Univariate analysis was conducted using, t-student, Mann-Whitney, or Chi-square tests as appropriate. Correlations between variables were assessed using the Spearman correlation coefficient.

Logistic and linear regression models were applied to assess the effect of biomarkers and baseline variables on patient functionality in the post-stroke period. ROC curves were plotted and the discriminative capacities of the models were assessed using standard measures. To test for changes in variables over time, one-way repeated measures analysis of variance (ANOVA) or the Friedman test were applied as appropriate. In a later phase, measured scores were transformed in percentages of the maximum score for each variable, to assess the relative change in functionality observed in different instruments. Two-way repeated measures ANOVA was applied, considering the interaction of time with the several functionality variables.

IBM SPSS Statistics version 23 (IBM Corp, Armonk, NY, USA) was used for statistical analysis, adopting a 5% significance level.

Funding

The principal investigator received no external funding to conduct this work. All costs beyond what would be routinely done in clinical practice were supported by the principal investigator (JPB).

PART C

EXPERIMENTAL WORK

CHAPTER 4

NEUROIMAGING AND BLOOD BIOMARKERS IN FUNCTIONAL PROGNOSIS AFTER STROKE

Published as:

Neuroimaging and Blood Biomarkers in Functional Prognosis after Stroke

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Acta Med Port 2016 Nov;29(11):749-754 DOI:10.20344/amp.7411

Título: Neuroimagem e Biomarcadores no Prognóstico Funcional de Doentes com Acidente Vascular Cerebral

Title: Neuroimaging and Blood Biomarkers in Functional Prognosis after Stroke

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RESUMO

Introdução: O acidente vascular cerebral é uma das principais causas de mortalidade e morbilidade em todo o mundo, associando-se a considerável incapacidade funcional. Atualmente sabe-se que tanto técnicas de neuroimagem como determinados biomarcadores fornecem informações úteis acerca da etiologia, decisão terapêutica, follow-up e prognóstico em doentes com acidente vascular cerebral isquémico. Assiste-se, porém, a um interesse particular na previsão do prognóstico vital em detrimento do prognóstico funcional. Antecipar o prognóstico funcional permitiria definir um programa de reabilitação adequado, objetivo e individualizado, com uma alocação de recursos mais eficiente. O presente trabalho tem como objetivo rever o conhecimento atual acerca do papel da neuroimagem e dos biomarcadores sanguíneos em fase aguda na previsão da recuperação funcional dos doentes que sobrevivem a um acidente vascular cerebral isquémico.

Material e Métodos: Revisão da literatura publicada entre 2005 e 2015, em língua inglesa, utilizando os termos "ischemic stroke", "neuroimaging" e "blood biomarkers".

Resultados: Foram selecionados nove artigos com base na leitura dos resumos.

Discussão: Técnicas de neuroimagem como a tomografia computorizada, a ecografia doppler transcraniana, a angiografia cerebral e a imagem de difusão por ressonância magnética apresentam potencial preditivo do prognóstico funcional do acidente vascular cerebral, nomeadamente através da avaliação do fluxo sanguíneo e do volume e localização da lesão, sobretudo quando usados em associação com a National Institutes of Health Stroke Scale. Vários biomarcadores têm sido estudados como potenciais marcadores de diagnóstico, estratificação de risco e previsão de prognóstico no acidente vascular cerebral, em particular a S100 calcium binding protein B, a proteína C-reativa, as metaloproteinases de matriz e o peptídeo natriurético cerebral.

Conclusão: Apesar de alguns biomarcadores e técnicas de neuroimagem revelarem capacidade preditiva, nenhum dos estudos com estas metodologias, isoladamente ou em associação, é capaz de sustentar a validação de um potencial modelo clínico preditivo de funcionalidade, revelando-se assim insuficientes na determinação precisa, nas primeiras horas após o acidente vascular cerebral, do prognóstico funcional aos três meses. Considera-se que são necessários mais estudos nesta área para o seu esclarecimento.

Palavras-chave: Acidente Vascular Cerebral; Biomarcadores/sangue; Neuroimagem; Prognóstico; Recuperação Funcional.

ABSTRACT

Introduction: Stroke remains one of the leading causes of morbidity and mortality around the world and it is associated with an important long-term functional disability. Some neuroimaging resources and certain peripheral blood or cerebrospinal fluid proteins can give important information about etiology, therapeutic approach, follow-up and functional prognosis in acute ischemic stroke patients. However, among the scientific community, there is currently more interest in the stroke vital prognosis over the functional prognosis. Predicting the functional prognosis during acute phase would allow more objective rehabilitation programs and better management of the available resources. The aim of this work is to review the potential role of acute phase neuroimaging and blood biomarkers as functional recovery predictors after ischemic stroke.

Material and Methods: Review of the literature published between 2005 and 2015, in English, using the terms "ischemic stroke", "neuroimaging" e "blood biomarkers".

Results: We included nine studies, based on abstract reading.

Discussion: Computerized tomography, transcranial doppler ultrasound and diffuse magnetic resonance imaging show potential predictive value, based on the blood flow study and the evaluation of stroke's volume and localization, especially when combined with the National Institutes of Health Stroke Scale. Several biomarkers have been studied as diagnostic, risk stratification and prognostic tools, namely the S100 calcium binding protein B, C-reactive protein, matrix metalloproteinases and cerebral natriuretic peptide.

Conclusion: Although some biomarkers and neuroimaging techniques have potential predictive value, none of the studies were able to support its use, alone or in association, as a clinically useful functionality predictor model. All the evaluated markers were considered insufficient to predict functional prognosis at three months, when applied in the first hours after stroke. Additional studies are necessary to identify reliable predictive markers for functional prognosis after ischemic stroke.

Keyword: Biomarkers/blood; Neuroimaging; Prognosis; Recovery of Function; Stroke.

INTRODUÇÃO

O acidente vascular cerebral (AVC) continua a ser uma patologia associada a elevada morbilidade e mortalidade. A maioria é de natureza isquémica e ocorre principalmente em indivíduos com idade superior a 65 anos, sendo a aterosclerose a causa mais frequente.

Atualmente a lesão vascular cerebral é considerada uma das principais causas de incapacidade funcional em todo o mundo.[1] A neuroplasticidade é superior nas primeiras 12 semanas após a lesão isquémica, o que confere uma janela relativamente estreita de atuação para a recuperação do doente.[2] Aproximadamente 70% dos doentes que sobrevivem a um AVC apresentam, na fase aguda, uma hemiparésia de predomínio braquial,[3] 20% destes doentes exigem cuidados institucionais durante os primeiros três meses após a lesão e 15% a 30% sofrem de incapacidade permanente.[4]

O prognóstico funcional em doentes com AVC é um tema de elevado interesse para clínicos e investigadores. O diagnóstico precoce e a identificação da etiologia são de crucial importância na previsão da recuperação dos múltiplos défices.[5] Antecipar o prognóstico funcional durante a fase aguda permitiria definir um programa de reabilitação adequado, objetivo, individualizado com uma alocação de recursos mais eficiente.

Os atuais modelos de classificação, baseados na etiologia do AVC, revelam-se insuficientes na previsão do prognóstico funcional.[4] A fiabilidade destes modelos poderá ser melhorada com recurso a biomarcadores sanguíneos (inflamação, hemostase, lesão neuronal ou glial e disfunção cardíaca) e a exames neuroimagiológicos.[6] O grande desafio da investigação atual é definir um modelo reprodutível,

sensível e exequível, preditor da funcionalidade do doente.

O presente trabalho tem como objetivo avaliar o potencial da neuroimagem e dos biomarcadores sanguíneos em fase aguda na previsão da recuperação funcional dos doentes que sobrevivem a um AVC isquémico.

MATERIAL E MÉTODOS

Os autores efetuaram uma revisão global da literatura com o objetivo de perceber qual o contributo da neuroimagem e dos biomarcadores no prognóstico funcional de doentes vítimas de AVC. A revisão foi complementada por uma pesquisa da literatura publicada entre os anos de 2005- 2015, em língua inglesa, com recurso à PubMed, utilizando os seguintes termos “ischemic stroke”, “neuroimaging” e “blood biomarkers” e os filtros “10 years”, “human species”, “english language” e “adult: 19+ years”.

RESULTADOS

Da pesquisa efetuada resultaram 43 artigos. Após leitura do resumo por dois autores foram selecionados nove artigos com relevância para o presente trabalho. Os critérios de escolha assentaram fundamentalmente na metodologia envolvendo conteúdos como AVC isquémico, estudo de proteínas no sangue periférico e/ou neuroimagem como fator de diagnóstico e/ou prognóstico pós AVC. Estudos cuja amostra incluísse outra patologia neurológica ou comorbilidade foram excluídos. Foi elaborada uma tabela resumo com as principais características dos nove estudos selecionados (Tabela 4.1).

DISCUSSÃO

Prognóstico e neuroimagem

A avaliação da imagem do parênquima cerebral em doentes com AVC é um tema de elevado interesse clínico, sendo a sua interpretação emergente e decisiva na intervenção clínica.

A tomografia computorizada (TC) é atualmente o exame imagiológico mais usado em contexto de urgência na avaliação destes doentes durante a fase aguda. Segundo o *National Institute of Neurological Disorders and Stroke* (NINDS), a TC, usada como uma ferramenta de rastreio para exclusão de hemorragia intracraniana antes da administração do *recombinant tissue plasminogen activator* (rt-PA), é o único instrumento eficaz na avaliação dos doentes submetidos a fibrinólise até três horas após o início dos sintomas.[7] Este estudo foi suportado pela quantificação do score ASPECTS (*Alberta Stroke Program Early CT Score*), baseado na avaliação da topografia da lesão cerebral. O score ASPECTS é obtido dividindo o território da artéria cerebral média (ACM) em 10 regiões de interesse, (M1-M6, I = ínsula, IC = cápsula interna, L = lenticular, e C = caudado). As áreas do território da ACM são assim ponderadas com base na importância funcional em detrimento da extensão da lesão. Uma pontuação de 10, pontuação máxima, é compatível com ausência de lesão visível no território da ACM. Trata-se um instrumento de avaliação do risco de transformação hemorrágica após fibrinólise, um potencial preditor de previsão da recuperação funcional[8] e apresenta correlação inversa com a gravidade do acidente vascular cerebral avaliada pela escala NIHSS (*National Institutes of Health Stroke Scale*).

A ecografia *doppler* transcraniana (EDT) é um meio complementar de imagem com grande interesse e potencial, sendo um método não invasivo, economicamente rentável, portátil e seguro, que permite a avaliação do fluxo sanguíneo intracerebral. Em oclusões da ACM apresenta alta sensibilidade, especificidade e valor preditivo positivo em estudos de comparação com a angiografia; é uma ferramenta importante para detetar oclusões vasculares intracranianas, bem como monitorizar o tratamento trombolítico através da existência ou não de recanalização cerebral.[9]

A angiografia cerebral convencional é de todos os exames de imagem o mais específico e sensível, permitindo visualizar oclusões agudas da ACM nas primeiras seis horas, bem como a

existência ou não de recanalização do fluxo sanguíneo. Permite uma excelente visualização da anatomia do vaso, da sua localização, extensão e grau de estenose, bem como da existência de circulação colateral. No entanto, o seu crescimento exponencial recente relaciona-se essencialmente com a sua aplicação terapêutica. Efetivamente, o tratamento endovascular para oclusões agudas de grande vaso intracraniano encontra-se já recomendado por todas as sociedades científicas internacionais.[10,11] Trata-se contudo de uma técnica invasiva e como tal não é usada para triagem.

Estudos referem que a recanalização espontânea ocorre maioritariamente nas primeiras 48 horas e, em 86% dos casos, ao fim de duas semanas. Esta avaliação hemodinâmica do fluxo sanguíneo arterial pode ser avaliada pela EDT, angio-TC ou angiografia tendo-se revelado como um importante preditor de bom resultado no AVC agudo.[12,13] No entanto, a recanalização espontânea tardia não tem habitualmente impacto clínico, tendo obrigado ao desenvolvimento de estratégias terapêuticas para recanalização em fase hiperaguda, inicialmente por fibrinólise endovenosa e, mais recentemente, por via endovascular.

A imagem de difusão por ressonância magnética (DRM) representa um avanço tecnológico na área da neuroimagem, sendo um exame não invasivo que permite avaliar a difusão das moléculas de água no tecido cerebral. Está principalmente indicada na avaliação e no diagnóstico de lesões cerebrais agudas em doentes sintomáticos onde a TC e ressonância magnética (RM) ponderada em T2/FLAIR (fluid-attenuated inversion recovery) não evidenciam alterações. Apresenta uma taxa de deteção de lesões isquémicas superior a 95% e tem sido demonstrada a sua alta precisão para delinear danos tecidulares irreversíveis nas primeiras horas após o início da lesão. A componente clínica (duração dos sintomas, alterações da capacidade de comunicação, capacidade motora e etiologia), parece estar diretamente correlacionada com o grau de alterações tecidulares cerebrais identificadas na DRM.[14] A DRM fornece, assim, informações clinicamente úteis no diagnóstico, etiologia, decisão terapêutica, prevenção, follow-up e no prognóstico funcional dos doentes após lesão cerebral aguda.[15]

Alterações cerebrais encontradas na RM convencional em doentes com lesão encefálica não apresentam valor preditivo robusto a longo prazo no prognóstico funcional do doente pós AVC.[16]

A avaliação imagiológica do volume da lesão mostrou correlação com o prognóstico funcional dos doentes.[17] Assim, verificou-se que a neuroimagem, em combinação com a NIHSS, apresenta maior sensibilidade na previsão da capacidade funcional em atividades de vida diária aos três meses após o AVC do que a NIHSS isoladamente.

Prognóstico e marcadores biológicos

O termo “biomarcador” tem sido comummente usado para avaliação da função biológica desde há aproximadamente 25 anos (a primeira referência identificada na Medline reporta-nos a 1977), e o seu uso disseminou-se na última década. A *National Institutes of Health* define biomarcador como uma

característica biológica que é objetivamente medida e avaliada como um indicador de processos biológicos normais, processos patogénicos ou respostas farmacológicas a uma intervenção terapêutica.[18]

Embora possa ser uma medida clínica ou imagiológica, o termo "biomarcador" é mais usado para moléculas encontradas nos fluidos corporais.[19] O seu doseamento deverá ser eficaz, específico e sensível à patologia em estudo.

Os biomarcadores podem ser classificados de acordo com a aplicação clínica pretendida. No AVC o seu doseamento auxilia no diagnóstico permitindo determinar a sua etiologia,[20] extrapolar o grau de deterioração neurológica precoce[21] e identificar os doentes que beneficiariam com intervenções específicas, incluindo hemicraniectomia descompressiva e recanalização arterial. Tem-se verificado um interesse crescente por parte da comunidade científica no uso dos biomarcadores na avaliação do prognóstico vital em detrimento do prognóstico funcional.[22]

A recanalização do fluxo sanguíneo arterial é um importante preditor de bom resultado no AVC agudo.[12] Até à data, não foi identificado qualquer biomarcador diretamente relacionado com a penumbra isquémica no homem; no entanto verificou-se que a concentração de glicose nestes tecidos é superior à de glutamato, sendo esta correlação inversa no tecido cerebral saudável.[21]

No AVC isquémico, cuja etiologia apresenta grande heterogeneidade, o principal objetivo consiste na procura de uma proteína seletiva correlacionada com a fisiopatologia do evento.[23] A falta de especificidade, a impermeabilidade da barreira hemato-encefálica (BHE) e o difícil doseamento no sangue periférico manifestam-se como condicionantes para essa identificação.

Têm sido desenvolvidos métodos para identificação de potenciais biomarcadores no sangue periférico assentando não só na procura de proteínas bem como em ácidos ribonucleicos específicos. Áreas como a proteómica e a genómica têm oferecido um importante potencial na identificação de moléculas cada vez mais sensíveis e específicas para uso clínico.

São identificados como biomarcadores de AVC moléculas envolvidas na hemostase aguda, como o fibrinogénio, os D-dímeros e o fator de Von Willebrand, e proteínas envolvidas na inflamação e na resposta imunitária, incluindo a proteína C-reativa (PCR), a interleucina-6 (IL-6), o fator de necrose tumoral α (FNT-α), a molécula de adesão da célula vascular 1 (VCAM 1), a molécula de adesão intercelular 1 (ICAM 1), anticorpos do recetor de N-metil-d-aspartato (NMDA) e metaloproteinases de matriz (MMPs).[24]

Entre os biomarcadores de AVC mais estudados, destacam-se a S100 *calcium binding protein B* (S100B), a enolase neuroespecífica (NSE), a proteína básica de mielina (MBP) e a proteína glial fibrilar ácida (GFAP). As MMPs estão envolvidas na destruição da integridade microvascular através da degradação da lâmina basal e matriz extracelular.

A proteína S100B é encontrada em altas concentrações nas células da glia e de Schwann. Vários estudos reportam um aumento significativo desta proteína no LCR (aproximadamente 40 vezes superior à do sangue periférico) logo após o AVC.[4,25] No sangue periférico, aumenta aproximadamente 12 horas após a lesão com um pico entre o segundo e terceiro dias e tem um tempo de semivida de duas horas.[26] Um estudo mostrou alterações da permeabilidade da BHE quando o conteúdo da proteína S100B excede 0,027 ng/mL.[27]

Em doentes com níveis de concentração de glutamato superiores a 200 μmol/l no plasma e superiores a 8,2 μmol/l no LCR, prevê-se uma deterioração neurológica precoce (com uma probabilidade de 92% e 93%, respetivamente). Manifesta-se assim como um mediador de lise celular e aumento do volume da lesão na DRM desde a admissão até às 72 horas pós lesão cerebral.[21]

Níveis elevados no sangue periférico de MMPs e S100B mostraram forte correlação com a transformação hemorrágica em doentes pós AVC isquémico[28]; uma concentração de S100B superior a 0,23 μg/l apresenta uma sensibilidade de 46% e especificidade de 82%.[29] Os níveis de PCR apresentam correlação positiva e os de colesterol HDL (high-density lipoprotein) uma correlação negativa com o insucesso na recanalização vascular precoce em doentes enfartados.[30]

Têm sido efetuados estudos na procura de potenciais marcadores do diagnóstico de AVC, estratificação de risco e previsão de prognóstico.[31] Ainda são poucos os biomarcadores que preenchem os requisitos necessários para serem introduzidos na prática clínica.[4] Embora alguns dos marcadores demonstrem capacidade preditiva, nenhum estudo foi suficiente para validar um modelo clínico baseado na utilização destes marcadores. A utilidade clínica dos biomarcadores como fator de prognóstico carece de estudos mais coerentes e válidos.[32]

Os trabalhos selecionados na pesquisa efetuada são realizados na sua totalidade em doentes com AVC; maioritariamente estudos prospetivos. Os biomarcadores de maior interesse na pesquisa são a proteína S100B, PCR, MMPs e o PNC (peptídeo natriurético cerebral); imagiologicamente os autores recorrem preferencialmente à DRM, e RM isoladamente ou em associação com a TC ou angiografia. O objetivo dos autores foca-se primordialmente na avaliação e correlação clínica dos biomarcadores cerebrais como diferenciadores de isquémia ou hemorragia cerebral, existência ou não de recanalização do fluxo sanguíneo, avaliação imagiológica do volume da lesão e severidade do AVC.

Nenhum dos estudos selecionados procurou estudar a funcionalidade dos doentes após AVC baseado na utilização de biomarcadores e/ou técnicas de imagem.

CONCLUSÃO

As técnicas de neuroimagem e biomarcadores fornecem informações clinicamente úteis na prevenção, diagnóstico, etiologia, decisão terapêutica, follow-up e prognóstico funcional dos doentes após lesão cerebral aguda.

Há interesse por parte da comunidade científica no uso de biomarcadores e neuroimagem na avaliação do prognóstico vital em detrimento do prognóstico funcional. A avaliação imagiológica do volume da lesão cerebral mostra correlação com o prognóstico funcional dos doentes após AVC. Níveis elevados no sangue periférico de MMPs e S100B revelam forte correlação com a transformação hemorrágica e predição de mau prognóstico funcional.

Contudo, apesar de alguns biomarcadores e técnicas de neuroimagem apresentarem capacidade preditiva, nenhum dos estudos com estas metodologias, isoladamente ou em associação, é capaz de sustentar a validação de um potencial modelo clínico preditivo de funcionalidade, revelando-se assim todos insuficientes na determinação precisa do prognóstico funcional aos 3 meses nas primeiras horas após o AVC.

CONFLITOS DE INTERESSE

Os autores declaram não ter qualquer conflito de interesse relativamente ao presente artigo.

FONTES DE FINANCIAMENTO

Os autores declaram não ter recebido subsídios ou bolsas para a elaboração do artigo.

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TABLES

Tabela 4.1 – Resumo das principais características dos nove estudos selecionados para a elaboração deste artigo de revisão.

Autor (ano)	Patologia estudo	Tipo de estudo	Amostra	Objetivo	Biomarcador	Exame de imagem
Wada M (208)23	AVC	Transversal	604 idosos da população geral	Determinar a relação entre a PCR, função cognitiva e a doença cerebral de pequenos vasos.	PCR	RM
Undén J (2009)20	AVC	Prospetivo multicêntrico	97 doentes (83 AVC isquémico; 14 AVC hemorrágico)	Avaliar a utilização clínica de vários potenciais biomarcadores cerebrais como diferenciadores de AVC isquémico e AVC hemorrágico na fase aguda.	S100B, EEN, PAFG, PCA-IPC	TC
Scarcello E (2011)25	AVC	Prospetivo	100 doentes (76 pós stenting artéria carotídea; 24 pós endarterectomia carotídea)	Avaliar a proteína S100B como possível marcador de lesão isquémica após tratamento de estenose carotídea.	S100B	DRM ou TC
Youn CS (2012)24	AVC	Transversal	96 doentes com AVC isquémico agudo	Avaliar a relação dos fatores inflamatórios com a severidade do AVC através da avaliação volumétrica da região enfartada.	PCR	DRM
Shimizu K (2013)17	AVC	Prospetivo	48 doentes com AVC isquémico agudo	Estudar a relação entre os níveis de vários biomarcadores após AVC e futura aterosclerose de grandes vasos cranianos.	PCR, IL-6, IL-18, FNT-α, MMP-2, MMP-9	Angiografia por RM
Montaner J (2012) 28	AVC	Transversal	915 doentes (776 AVC isquémico, 139 AVC hemorrágico)	Estudar o valor preditivo de vários marcadores sanguíneos na diferenciação entre AVC isquémico e AVC hemorrágico.	PCR, D-dimeros, sRPGA, MMP9, S100B, BNP, NT-3, caspase-3, chimerin-II, secretagogin, cerebellin, NPY	TC
Montaner J (2012)22	AVC	Prospetivo	896 doentes com AVC	Estudar a relação entre os níveis de BNP no plasma e alterações neurológicas / morte após AVC (isquémico e hemorrágico).	BNP	-
Tu WJ (2013)31	AVC	Prospetivo	189 doentes com AVC isquémico	Avaliar vários biomarcadores como fatores preditivos do prognóstico e	PNC, NT-pro-PNC, cortisol, copeptina	-

Autor (ano)	Patologia estudo	Tipo de estudo	Amostra	Objetivo	Biomarcador	Exame de imagem
				mortalidade após AVC isquémico.		
Koga M (2013)30	AVC	Retrospetivo	70 doentes com AVC isquémico tratados com rt-PA	Estudar os fatores associados ao insucesso da recanalização precoce após terapia intravenosa com rt-PA.	PCR, HDL	Angiografia por RM

S100B: S100 calcium-binding protein B; EEN: Enolase especifica neuronal; PAFG: Proteína ácida fibrilar glial; PCA-IPC: Proteína C ativada – inibidor do complexo proteína C; PCR: Proteína C reativa; IL- 6: Interleucina-6; IL-8: Interleucina-8; FNT-α: Fator de necrose tumoral α; MMP-2: Metaloproteinases de matriz 2; MMP-9: Metaloproteinases de matriz 9; sRPGA: Solúvel recetor dos produtos finais de glicosilação avançada; BNP: Brain natriuretic peptide; NT3: Neurotrofina 3; NPY: Neuropeptideo Y; NT pro-PNC: N-terminal peptídeo natriurético cerebral; rt-PA: Ativador do plasminogénio tecidular recombinante, HDL: Lipoproteína de alta intensidade; DRM: Difusão por ressonância magnética; TC: Tomografia computorizada; RM: Ressonância magnética.

CHAPTER 5

TRANSCULTURAL ADAPTATION AND VALIDATION OF THE PORTUGUESE VERSION OF THE STROKE UPPER LIMB CAPACITY SCALE

Published as:

Assessing upper limb function: transcultural adaptation and validation of the Portuguese version of the Stroke Upper Limb Capacity Scale

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BMC Sports Science, Medicine and Rehabilitation (2017) 9:15 DOI 10.1186/s13102-017-0078-9

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ABSTRACT

Background: Brachial hemiparesis is one of the most frequent sequelae of stroke, leading to important functional disability given the role of the upper limb in executing activities of daily living (ADL). The Stroke Upper Limb Capacity Scale (SULCS) is a stroke-specific assessment instrument that evaluates functional capacity of the upper limb based on the execution of 10 tasks. The objective of this study is the transcultural adaptation and psychometric validation of the Portuguese version of the SULCS.

Methods: A Portuguese version of the SULCS was developed, using the process of forward-backward translation, after authorisation from the author of the original scale. Then, a multicentre study was conducted in Portuguese stroke patients (n=122) to validate the psychometric properties of the instrument. The relationship between sociodemographic and clinical characteristics was used to test construct validity. The relationship between SULCS scores and other instruments was used to test criterion validity.

Results: Semantic and linguistic adaptation of the SULCS was executed without substantial issues and allowed the development of a Portuguese version. The application of this instrument suggested the existence of celling effect (19.7% of participants with maximum score). Reliability was demonstrated through the intraclass correlation coefficient of 0.98. As for construct validity, SULCS was sensible to muscle tonus and aphasia. SULCS classification impacted the scores of the Motor Evaluation Scale for Upper Extremity in Stroke (MESUPES) and the Stroke Impact Scale (SIS).

Conclusions: The present version of SULCS shows valid and reliable cultural adaptation, with good reliability and stability.

Keywords: Stroke; Stroke Upper Limb Capacity Scale; Upper limb; Disability; Functionality; Hemiparesis

BACKGROUND

Stroke continues to be associated with high morbidity and mortality worldwide. In Portugal, the mortality rate from cerebrovascular diseases decreased from 71.9 deaths per 100,000 inhabitants in 2009 to 54.6 deaths per 100,000 inhabitants in 2013 [1]. The majority of strokes were of ischaemic aetiology, occurring mostly in individuals >65 years-old, with atherosclerosis as the main cause [2].

Brain lesions due to cerebrovascular diseases are, currently, one of the leading causes of disability [3]. Approximately 70% of patients that survive stroke present hemiparesis with brachial predominance in the acute phase [4], 30% of those require inpatient care during the first 3 months and, ultimately, 15–30% of patients show permanent disability [5]. Approximately 70% of patients with mild to moderate paresis recover some degree of manual dexterity within the first 6 months, while patients with paresis of the limb with reduced muscle strength do not recover [6].

The upper limb is crucial in executing activities of daily living (ADL) [6] and, therefore, there is a need for an assessment instrument capable of evaluating and quantifying upper limb functionality after stroke. Several instruments have been developed to assess motor, sensitive, and functional ability after stroke [7,8], including the Jebsen-Taylor Hand Function Test [9], the Box and Block Test [10], and the Frenchay Arm Test [11]. However, all these instruments require some degree of hand functioning and, as such, are not adequate for patients with severe hand disability. Other instruments such as the Research Arm Test [12] and the Upper Limb Motor Assessment Scale [13] evaluate other parameters beyond functional capacity, which hinders the interpretation of functional capacity results [7].

The Stroke Upper Limb Capacity Scale (SULCS) was developed in this context as an easy-to-use, unidimensional, hierarchical, and internally consistent scale that assesses upper limb capacity after stroke. It was the first assessment instrument that included items evaluating both basic upper limb functioning (activities that require reduced or no hand functioning) and more demanding upper limb functioning (activities that require intensive distal functioning) [7, 14].

The objective of this study is the transcultural adaptation and psychometric validation of the Portuguese version of the SULCS in a sample of Portuguese stroke patients.

METHODS

Study design and sample

This was a multicentre study conducted in the Centre region of Portugal, in patients with history of stroke (both of ischaemic and/or haemorrhagic nature). A total of 122 patients agreed to participate

in the study, most of whom had permanent functional disability. The clinical procedures of the study were conducted between May 2014 and April 2015.

All participants were evaluated by healthcare professionals specialised in rehabilitation in the context of stroke or other neurological conditions. Beyond the Portuguese version of SULCS and the sociodemographic questionnaire, the following assessment instruments were used: generic quality of life scale (EuroQol five dimensions questionnaire [EQ-5D]), specific stroke scale (Stroke Impact Scale [SIS]), and specific upper limb functionality scale (Motor Evaluation Scale for Upper Extremity in Stroke [MESUPES]). All these instruments were previously validated for use in the Portuguese population.

The study was conducted according to the precepts of the Declaration of Helsinki and the Oviedo Convention. The study protocol and data collection instruments were approved by the Ethics Committee of the Faculty of Medicine of the University of Coimbra (reference letter 104-CE-2014). This assessment constituted the basis for approval of the study in all participating centres. All participants provided their written informed consent prior to enrolment in the study.

Measures

Stroke Upper Limb Capacity Scale

SULCS is the first assessment instrument that includes items evaluating both basic upper limb functioning (activities that require reduced or no hand functioning) and more demanding upper limb functioning (activities that require intensive distal functioning) [7,14]. This instrument can be used in men and women with both left and right hemiplegia, and in both ischaemic or haemorrhagic stroke [14]. SULCS assessments are short (approximately six minutes) and are based on 10 specific activities that are related to the patients' ADLs. Three items evaluate proximal functioning (in which there is no active function from the hand and fist), four items evaluate functioning that requires basic control of the fist and fingers, and three items evaluate advanced distal functioning [6,7,14].

SULCS assessments can use "start and stop" rules with which it is possible to forgo the assessment of tasks that were previously successfully executed or to interrupt the evaluation when the patient is incapable of executing certain tasks. In this instrument, tasks are unidimensional and hierarchically ordered by increasing difficulty of execution. Scoring is dichotomous: 0 points if it is not possible to execute the task or 1 point if the task is properly executed. The sum of the scores from each task leads to a total score that varies from 0–10 points, with higher scores indicating better functioning. Results from SULCS assessments can be summarised in the following categories: "no hand functioning" (0–3 points), "basic hand functioning" (4–7 points), "good hand functioning" (8–10 points) [6]. Contrary to other instruments previously used in this context, SULCS can categorise patients

according to their proximal and distal functioning, which provides value insight for patient prognosis in terms of functional recovery.

EuroQol five dimensions questionnaire

EQ-5D allows the general assessment of health-related quality of life [15]. This instrument evaluates several dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. It also includes a self-evaluation component, in which the respondents evaluate their overall health status through a visual analogue scale (EQ-VAS), ranging from 0 (worse health status imaginable) to 100 (best health status imaginable). The Portuguese validated version of EQ-5D and the corresponding valuing system were used in this study [16,17].

Stroke Impact Scale

SIS is a stroke-specific instrument designed to assess multidimensional stroke outcomes; it consists of 65-items grouped in the following categories: strength (four items), memory and thinking (eight items), emotion (nine items), communication (seven items), participation (12 items), mobility (10 items), hand function (five items), ADLs/instrumental ADLs (9 items), and recovery (1 item) [18,19]. The Portuguese validated version of SIS was used in this study [19].

Motor Evaluation Scale for Upper Extremity in Stroke (MESUPES)

MESUPES was designed to evaluate the quality of upper limb movements after stroke. It consists of 17 items, 8 of which refer to proximal upper limb functioning and 9 to distal upper limb functioning [20,21].

Translation and transcultural adaptation

SULCS was developed in 2001 at the Sint Maartenskliniek Rehabilitation Centre, in Nijmegen, The Netherlands. Between 2001 and 2008, SULCS was applied to 546 patients hospitalised in this centre and in 2010 the data from these assessments were used to evaluate the reliability, sensitivity, and validity of the scale. The results of this analysis revealed that SULCS has outstanding psychometric properties [7]. The scale has since been translated and validated for the English language and a French validation is in progress.

After authorisation from the author of the original SULCS, a Portuguese version of the scale was developed, using the process of forward-backward translation [22]. The process of forward translation consisted of an initial preparation of two translations, completed by two independent Portuguese bilingual translators, one translator was a professional translator and the other was a PhD and teacher

of English. Then, a consensus version was prepared by two of the authors (PLF and JPB). This consensus version was then back-translated by a native English translator. The back-translated version was evaluated by the authors PLF, JPB, and JPP to verify agreement with the original instrument and, then, a final version of the Portuguese SULCS translation was prepared. Subsequently, a Portuguese expert in the field of rehabilitation conducted a clinical review to obtain a more specialised translation, which would be easier to understand by employing language with which the patients were more familiar.

Statistical analyses

The acceptability of the scale was tested through the quantification of missing data and the distribution of the sample by the various categories of the scale. The following hypothesis was formulated:

- H_1: The SULCS scale presents no significant missing data and its distribution is spread over the various categories.

Concordance between observers was evaluated in 41 participants. Each of those participants was subject to two evaluations by different healthcare professionals. Cohen's kappa coefficient and the criteria defined by Landis and Koch were used for this analysis [15].

To test the construct validity of SULCS, criteria derived from sociodemographic and clinical variables in known samples were used. The following hypotheses were tested:

- H_2: Patient gender impacts SULCS score.
- H_3: Patient age impacts SULCS score.
- H_4: Stroke aetiology (haemorrhagic/ischaemic) impacts SULCS score.
- H_5: Left/right lateralisation of the affected limb impacts SULCS score.
- H_6: Tonus changes impact SULCS score.
- H_7: Presence of communication impairment (aphasia) impacts SULCS score.

These hypotheses were tested using Chi-square tests, as well as tests for the comparison of means (*t*-Student for two independent samples or ANOVA for more than two samples). *Post-hoc* multiple comparison analyses were used when applicable.

To test criterion validity, SULCS was categorised into “no hand functioning” (0–3 points), “basic hand functioning” (4–7 points), and “good hand functioning” (8–10 points), and then compared with EQ-5D, SIS, and MESUPES, with the objective of testing the following hypotheses:

- H_8: Patients with good hand functioning according to SULCS show higher EQ-5D scores.
- H_9: Good hand functioning according to SULCS is highly associated with SIS.
- H_{10}: SULCS scores are highly associated with MESUPES total scores.

Statistical analyses were performed with IBM SPSS Statistics for Windows, Version 23.0. (IBM Corp, Armonk, NY, USA). A 5% level of significance was adopted.

RESULTS

Semantic and linguistic adaptation

The changes suggested after the expert review were scarce and based on clinical and linguistic criteria. In the original SULCS instrument there was a reference to the term "affected forearm", which had been equivalently translated and was changed during the expert review to the Portuguese equivalent of "affected limb". The remaining changes consisted of verb conjugation corrections. Therefore, content validity was obtained.

Study sample

Data obtained from the sociodemographic questionnaire of the 122 participants are presented in **Table 5.1**. Mean age in the study sample was 67.8±12.1 years and mean time after stroke was 14.0 months. There was no significant predominance in terms of gender or laterality. Most participants had had stroke of ischaemic origin, and most showed no discernible spasticity or aphasia.

Table 5.2 presents the descriptive statistics for the various assessment instruments used in the study. Perception of health-related quality of life was fairly low in the study population, as suggested by the mean EQ-5D score of 0.21. This value decreased with advancing age: 0.33 (<50 years), 0.27 (50–64 years), 0.18 (65–74 years), and 0.15 (≥75 years).

According to SIS scores, the dimensions that showed higher impairment after stroke in this population were hand function (32.4%), strength (41.2%), and ADLs (45.8%). Communication was the dimension evaluated by SIS in which participants showed better results.

Mean SULCS score was 6.0. Most participants (43.3%) showed good hand functioning, 24.6% showed basic hand functioning, and 32.0% showed no hand functioning.

In the affected limb, according to MESUPES scores, there was greater functional impairment at the hand rather than the shoulder (47.9% and 73.9%, respectively).

Acceptability and distribution

Since SULCS is applied by healthcare professionals, there were no comprehension issues or any other difficulty in conducting the assessments; this is reflected by the absence of missing data (Hypothesis H_1). The distribution of the sample included all SULCS categories: no hand function (32.0%), basic hand functioning (24.6%), and good hand functioning (43.3%). However, the highest SULCS score (10) was registered in 24 patients (19.7%), thus showing evidence of a ceiling effect (according to a 15% criterion).

Reliability

SULCS showed a 0.984 intraclass correlation coefficient. Since SULCS allows categorisation (no hand functioning, basic hand functioning, and good hand functioning), a 0.886 Cohen's kappa coefficient was also calculated.

Construct validity

Construct validity was tested by assessing how different values of sociodemographic and clinical characteristics impacted SULCS scores, as shown in **Table 5.3**. When considering hypotheses H_2 to H_7, only the variables change in muscle tonus and the presence of aphasia were determinants for hand functioning as measured by SULCS (Hypothesis H_6).

Criterion validity

To test criterion validity, SULCS scores (in categorised from) were compared with scores from EQ-5D, SIS, and MESUPES, as shown in **Table 5.4**. That is, we tested whether different functional categories given by SULCS correspond to different average scores given by EQ-5D, SIS, and MESUPES.

Participants with good hand functioning according to SULCS showed better overall health status, as measured through EQ-5D (mean EQ-5D of 0.36), than the remaining groups (Hypothesis H_8).

All dimensions of SIS were significantly impacted by SULCS scores (Hypothesis H_9); there were particularly strong effects for the dimensions of recovery, ADLs, mobility, hand function, and participation (all $p<0.001$). For all these dimensions, participants with good hand functioning showed higher scores in SIS, as compared to the remaining groups. For the dimensions of memory, emotion, and communication, as would be expected, the effects were of lesser magnitude.

The MESUPES scores were also impacted by SULCS scores, including both dimensions and the total score (Hypothesis H_{10}).

DISCUSSION

Stroke has a reported incidence of 1.9% in the general population, but is more frequent in men and individuals with age 65 to 74 years-old [23]. Ischaemic aetiologies represent the majority of strokes (87%, thrombotic or embolic), while haemorrhagic aetiologies represent a small fraction of cases (13%, intracerebral or subarachnoid) [24]. In this study, the mean age was over 65 years and there was a predominance of ischaemic stroke, as expected according to the literature. However, we found no statistically significant differences in terms of gender predominance or laterality. It should be also

highlighted that there was a mean time from stroke of approximately 14 months and spasticity and aphasia were not particularly clinically relevant in this population.

Stroke continues to be one the main causes of health-related quality of life impairment in the country [25], which is reflected in the EQ-5D scores from this sample (EQ-5D of 0.21). These findings are consistent with previous studies, and further highlight the medical and social impact of stroke in the Portuguese population. However, despite the impact of stroke in the Portuguese population there is not yet a validated instrument to specifically assess upper limb functioning in these patients. The development of such functional evaluation tools is crucial to improve the clinical management of stroke patients and to allow the development of clinical research in rehabilitation medicine. SULCS is an easy-to-use, unidimensional, hierarchical, and internally consistent scale that evaluates upper limb functioning after stroke and can provide valuable insight in both clinical practice and clinical research contexts.

SIS scores were significantly impacted by SULCS classification for all dimensions, with particularly stronger impact for the dimensions of strength, ADLs, mobility, hand function, and participation. These findings can be explained by the fact that most of the tasks alluded by SIS need proper upper limb function to be adequately executed. The recovery dimension was also impacted by the SULCS classification of participants, which highlights the importance of upper limb functional recovery for general recovery after stroke. SULCS classification did not, however, impacted the dimensions of memory, emotion, and communication, as would be expected since these aspects are not particularly dependent on upper limb functioning.

MESUPES scores were also strongly impacted by SULCS classification for both dimensions as well as the total score. Such findings were expected, since SULCS and MESUPES evaluate highly-related types of functioning and, therefore, these results confirm the capacity of this version of SULCS in establishing upper limb functionality.

In terms of EQ-5D results, this population showed substantially impaired quality of life, but, interestingly, average SULCS scores were only indicative of moderate upper limb functional impairment (with mean SULCS score within the basic hand functioning category) [6]. These findings highlight the importance of using specific instruments to assess the several domains that can impact a patient's quality of life and health status, since general quality of life assessments do not always accurately represent aspects that play important roles in performing ADL's, such as upper limb functioning.

Several factors associated with worse prognosis after stroke have been described in the literature, including advanced age, right hemisphere involvement, lesions of haemorrhagic nature, and cognitive impairment [26–28]. In this study, however, there were no statically significant associations between age, gender, aetiology, and laterality and upper limb functional capacity as measured by SULCS. These

results can be explained by the fact that SULCS is a highly-specific instrument aimed at evaluating upper limb functioning and not overall patient functionality or health status (as assessed in previous studies). As for the relationship between gender and functional recovery after stroke, this study is agreement with previous evidence, indicating that gender is not significantly associated with functional prognosis [26,28].

The presence of spasticity in the upper limbs after stroke has been associated with impaired functionality and high levels of dependence [29]. In this study, patients with higher degree of spasticity showed lower upper limb functional capacity (with significantly lower SULCS scores), as expected. The difference in SULCS scores for patients showing spasticity vs. non-spastic patients was highly significant ($P<0.001$), despite the fact that only 23% of the study population showed spasticity in the upper limbs, thus, further emphasising the relevance of this difference. Further studies should explore the effect of spasticity on long-term upper limb functioning as measured by SULCS.

Patients with aphasia showed significantly lower upper limb functional capacity according to SULCS scores. In this case, however, the findings should be interpreted with caution, since there is a potential for bias due to the communication deficits of patients with aphasia and the inherent difficulties in applying the assessment instrument.

This study has limitations that should be considered. The study population was relatively heterogeneous (particularly in terms of age distribution and time since acute stroke). The multicentre design has some disadvantages to consider, particularly the larger number of healthcare professionals involved in the study procedures, which may increase the potential for subjectivity in the assessments. Patients with aphasia were enrolled, including those with expression aphasia, which might pose a bias in interpreting the results from assessment scales. The population also had substantially impaired overall health status, which can bias the results towards lower quality of life and impaired functioning.

CONCLUSIONS

The process of translation and transcultural adaptation of SULCS to the Portuguese population was performed without substantial issues, with high concordance between translation and expert review.

In terms of sociodemographic and clinical factors, the instrument was sensible to muscle tonus and aphasia. There was high concordance between observers, which demonstrates reliability.

Health-related quality of life decreased with advancing age in this patient population, but this factor was not reflected in hand functioning.

SULCS classification impacted MESUPES and SIS dimensions, with stronger impacts in the dimensions of strength, ADLs, mobility, hand function, and participation. These data provided the basis to confirm both construct and criterion validity.

Therefore, the present version of SULCS is validated for use in the Portuguese population.

Ethical Approval and Consent to participate

The study was conducted according to the precepts of the Declaration of Helsinki and the Oviedo Convention. The study protocol and data collection instruments were approved by the Ethics Committee of the Faculty of Medicine of the University of Coimbra (reference letter 104-CE-2014). This assessment constituted the basis for approval of the study in all participating centres. All participants provided their written informed consent prior to enrolment in the study.

Authors' contributions

JPB and PF designed the study; JPB, PF, JPP coordinated the process of translation and transcultural adaptation; JPB, SO collected the data; JPB, PF contributed to data analysis and interpretation; JPB, SO drafted the manuscript; PF, JPP, JPB conducted critical analysis of the contents of the manuscript; and all authors reviewed and approved the final manuscript.

Acknowledgements

The authors thank all the healthcare professionals involved in the implementation of this study at the various clinical centres (Centro de Medicina e de Reabilitação da Região Centro, Hospital São João Baptista e Hospital da Misericórdia da Mealhada). The authors also thank Tiago Campos (ARC Publishing) for providing editorial assistance.

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TABLES

Table 5.1 – Demographic and clinical characteristics of the study population.

Variable	Study population (n=122)
Gender, n (%)	
Male	65 (53.3)
Female	57 (46.7)
Age (years)	
Mean ± standard deviation	67.8 ± 12.1
Min	32
Max	94
Time after stroke (months)	
Mean ± standard deviation	14.0 ± 16.5
Median (min, max)	10.3 (1.6, 131.0)
Trimmed Mean 5%	11.4
Type of stroke, n (%)	
Ischaemic	81 (66.4)
Haemorrhagic	25 (20.5)
Undetermined	16 (13.1)
Laterality, n (%)	
Right	56 (45.9)
Left	65 (53.7
Tonus, n (%)	
Spastic	28 (23.0)
Aphasia, n (%)	
Yes	38 (32.1)

Table 5.2 – Descriptive statistics for the EQ-5D, SIS, SULCS, and MESUPES scales in the study population (n=122).

Variable	Minimum	Maximum	Mean	Standard deviation
EQ-5D				
Dimensions	-0.49	1.0	0.21	0.3
EQ-VAS	20.0	90.0	51.7	16.5
SIS				
Recovery	10.0	95.0	53.0	20.4
Strength	12.5	100.0	41.2	19.1
Memory	0.00	100.0	73.4	25.1
Emotion	33.3	80.6	57.7	10.5
Communication	0.00	100.0	80.2	24.6
Activities of daily living	4.2	100.0	45.8	24.7
Mobility	2.5	100.0	49.8	27.5
Hand function	0.0	100.0	32.4	33.0
Participation	11.1	100.0	53.9	20.4
SULCS	0.0	10.0	6.0	3.3
MESUPES				
Hand	0.0	2.0	47.9	36.9
Shoulder	0.0	5.0	73.9	33.0
Total	0.0	3.4	65.6	32.7

EQ-5D = EuroQol five dimensions questionnaire; MESUPES = Motor Evaluation Scale for Upper Extremity in Stroke; SIS = Stroke Impact Scale; SULCS = Stroke Upper Limb Capacity Scale

Table 5.3 – Mean SULCS scores according to sociodemographic and clinical characteristics of the study population.

Variable	Value	N	Mean ± SD	| *t* |	p-value
Gender	Male	65	6.15 ± 3.22	0.698	0.486
	Female	57	5.74 ± 3.37		
Age	<65 years old	50	5.90 ± 3.30	0.165	0.869
	≥65 years old	72	6.00 ± 3.29		
Type of stroke	Ischaemic	81	5.93 ± 3.37	0.061	0.952
	Haemorrhagic	25	5.88 ± 3.14		
Laterality	Right	56	6.01 ± 3.51	0.081	0.936
	Left	65	5.97 ± 3.09		
Tonus	Spastic	28	3.32 ± 2.68	5.265	<0.001
	Non-spastic	79	6.79 ± 3.09		
Aphasia	Yes	38	4.75 ± 3.44	2.533	0.013
	No	84	6.44 ± 3.13		

SD = Standard deviation; SULCS = Stroke Upper Limb Capacity Scale

Table 5.4 – Mean EQ-5D, SIS, and MESUPES scores according to SULCS scores (in categorised form).

Variable	SULCS category			*F*	p-value	Post-hoc multiple comparison
	No hand functioning [1]	Basic hand functioning [2]	Good hand functioning [3]			
EQ-5D						
Dimensions	0.01 ± 0.29	0.20 ± 0.25	0.36 ± 0.24	20.75	<0.001	1<2<3
EQ-VAS	48.2 ± 14.6	47.7 ± 17.4	56.6 ± 16.2	4.32	0.015	1=2<3
SIS						
Recovery	46.1 ± 17.9	48.5 ± 20.2	60.6 ± 20.1	7.29	0.001	1=2<3
Strength	27.4 ± 12.9	39.6 ± 15.9	52.4 ± 17.7	27.95	<0.001	1<2<3
Memory	74.0 ± 24.8	69.0 ± 30.5	75.5 ± 22.2	0.66	0.516	
Emotion	57.6 ± 10.3	55.2 ± 11.1	59.3 ± 10.3	1.46	0.236	
Communication	77.4 ± 27.8	79.4 ± 27.8	82.7 ± 20.0	0.54	0.586	
ADL	29.7 ± 18.9	40.7 ± 22.2	60.5 ± 21.3	26.01	<0.001	1<2<3
Mobility	32.8 ± 23.4	46.6 ± 25.7	64.2 ± 23.5	19.53	<0.001	1<2<3
Hand function	2.1 ± 5.1	23.5 ± 22.4	59.8 ± 26.9	87.06	<0.001	1<2<3
Participation	45. 9 ± 15.8	49.9 ± 21.5	62.1 ± 20.1	8.96	<0.001	1=2<3
MESUPES						
Hand	0.05 ± 0.14	0.45 ± 0.3	0.79 ± 0.2	180.52	<0.001	1=2<3
Shoulder	0.33 ± 0.24	0.84 ± 0.1	0.99 ± 0.0	205.52	<0.001	1=2<3
Total	0.24 ± 0.19	0.72 ± 0.1	0.93 ± 0.1	289.65	<0.001	1=2<3

EQ-5D = EuroQol five dimensions questionnaire; MESUPES = Motor Evaluation Scale for Upper Extremity in Stroke; SIS = Stroke Impact Scale; SULCS = Stroke Upper Limb Capacity Scale

CHAPTER 6

S100B PROTEIN AS A PREDICTOR OF POST-STROKE FUNCTIONAL OUTCOME

Published as:

S100β protein as a predictor of post-stroke functional outcome: a prospective study

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J Stroke Cerebrovasc Dis. 2018 Jul;27(7):1890-1896.

DOI: 10.1016/j.jstrokecerebrovasdis.2018.02.046

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ABSTRACT

Background: Stroke is one of the leading causes of disability worldwide. Early prediction of post-stroke disability using clinical models is of great interest, especially in the rehabilitation field. Although some biomarkers and neuroimaging techniques have shown potential predictive value, there are still insufficient data to support their clinical utility in predicting post-stroke functional recovery. To assess the value of serum biomarkers (CRP, D-Dimer, fibrinogen, and S100β protein), in predicting medium-term (12 weeks) functional outcome, in patients with acute ischemic stroke.

Methods: This is an observational, prospective study in a sample of patients hospitalised for ischaemic stroke (n=131). Peripheral blood levels of biomarkers of interest were determined at admission (C-reactive protein, D-dimer, and fibrinogen) or at 48 hours post-stroke (S100β protein). Functional status was accessed at 48 hours and 12 weeks post-stroke, using the modified Rankin Scale (mRS).

Results: S100β protein levels measured at 48 hours were significantly associated with mRS scores at 12 weeks (OR=1.005, 95%CI [1.005–1.007]; $P<0.001$). This association that was not seen for the remaining biomarkers of interest. The S100β cut-off for poor functionality at 12 weeks was ≥140.5 ng/L (sensibility 83.8%; specificity 71.4%; AUC=0.80, 95%CI [0.722, 0.879]).

Conclusions: S100β levels in peripheral blood at 48 hours post-stroke reflect acute stroke severity and predict functional outcome at 12 weeks with a cut-off value of 140.5 ng/L. The value of S100β as predictor of functional recovery after-stroke should be emphasised in further clinical research and clinical practice.

Keywords: Stroke; Biomarkers; S100β; Rehabilitation; Functionality

INTRODUCTION

Stroke is one of the leading causes of functional disability worldwide. Ischaemic events represent approximately 85% of acute stroke cases [1]. In the presence of acute stroke, it is crucial to establish an early diagnosis, with proper identification of aetiology, and to provide timely thrombolytic treatment, which is very time-sensitive, to prevent or, at least, reduce potential functional deficits [2].

Advances in stroke treatment led to the need to assess the actual clinical effectiveness of such interventions. Beyond the conventional measures of survival and recurrence prevention, it is important to ascertain the quality of patient recovery, using specific functional assessment scales to evaluate the value of new therapeutic strategies [3]. Several recent studies tried to identify early predictors of functional prognosis after stroke [1,4,5]. Such predictors would be highly valuable to guide rehabilitation treatment, allowing the development of effective, individualised rehabilitation programs and, ultimately, providing a means for more efficient resource allocation [6]. Unfortunately, accurate predictive models of functional prognosis in patients with acute stroke are yet to be established [7].

In the clinical management of stroke, the use of biomarkers (including inflammation, haemostasis, neural or glial lesion and cardiac dysfunction) is important to establish precise diagnosis, to guide treatment strategies, and to estimate vital and functional prognosis. Biomarkers could be particularly valuable in establishing the "ischemic penumbra" area [6]. However, to date, no biomarker was found to be directly related to the cerebral ischaemic penumbra [8]. The slow release of glial and neuronal proteins across the blood brain barrier (BBB) and their lack of specificity could explain the difficulty in finding these biomarkers [6].

Acute phase biomarkers, such as C-reactive protein (CRP), fibrinogen, D-dimer, and, especially S100β protein, have been investigated and highlighted as potential predictors of structural brain injury, mortality, and functionality after stroke [5,6,9]. The S100β protein is a small calcium-binding protein of the S100 family. It is mainly expressed in the nervous system in astrocytes, mature oligodendrocytes, dendritic cells, and Schwann cells [10], but it may also be expressed in other locations, including kidney epithelial cells, ependymocytes, chondrocytes, adipocytes, and melanocytes [11]. S100β is thought to play an important role in inflammatory response in central nervous system (CNS) [2]. In normal concentrations, it stimulates the proliferation of glial cells and the regeneration of damaged nerves. Some authors argue that low S100β concentrations have a protective effect in the CNS, preventing neuronal degeneration and ensuring neuronal maintenance and survival. On the other hand, high S100β concentrations are indicative of neuronal toxicity [2], through the production of reactive oxidative species (cytochrome C release) and induction of apoptosis [11].

Over the past decade, S100β has emerged as a candidate for peripheral biomarker of BBB permeability and CNS damage. Wiesmann et al define the mean S100β serum concentration in healthy adults as approximately 65 ng/L, with concentrations >27 ng/L associated with changes in BBB

permeability [12]. Several studies also report a significant increase of this protein in the cerebrospinal fluid (approximately 40 times higher than serum concentration) after stroke [2,7–14]. In peripheral blood, S100β increases substantially up to 48 hours post-stroke, with a peak occurring between the second and third days [2,7–15]. Serum concentration >230 ng/L is associated with haemorrhagic transformation, with a sensitivity of 46% and specificity of 82% [16].

Although acute phase biomarkers have been increasingly used in developing predictive models of vital prognosis or haemorrhagic transformation, few studies specifically evaluated medium to long-term functional outcome [5]. Therefore, there is a need to develop specific predictive models of patient functional prognosis after stroke, which would be highly valuable in informing treatment decisions and guiding rehabilitation programs.

This study aims to assess the potential of a panel of serum biomarkers (including CRP, D-Dimer, fibrinogen, and S100β) in patients with acute ischemic stroke to predict medium-term (12 weeks) functional outcome.

MATERIALS AND METHODS

Study design and sample

This is an observational, prospective study in a sample of patients hospitalised with stroke, between April 2015 and April 2016, in a Stroke Unit of a Portuguese tertiary care hospital. Patients (ages: 18–85 years) could be included if they had ischemic stroke in the territory of the middle cerebral artery (MCA), established through clinic and imagiological evaluation. Exclusion criteria were as follows: (a) not going to the emergency room (ER) within 3 hours of symptom onset, (b) haemorrhagic transformation [17], (c) presence of premorbid functional impairment, and (d) presence of neurological, inflammatory (acute or chronic), or neoplastic comorbidities. Patients in which it was not possible to collect peripheral blood or conduct cranioencephalic computed tomography (CT) scan were also excluded.

The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Coimbra (reference letter 104-CE-2014). All patients or their legal representatives provided written informed consent before inclusion in the study.

Assessments

Patients were observed in three stages: (1) at admission to the ER, (2) 48 hours after stroke, and (3) 12 weeks after stroke. At each stage, different clinical, laboratory, and functional assessments were performed.

Clinical and laboratory evaluation

A neurologist observed patients on study inclusion, corresponding to a maximum period of 6 hours after symptom onset (only patients that presented to the ER within 3 hours of symptom onset were included as mentioned above). Peripheral blood was collected (prior to any fibrinolytic/thrombolytic therapy was introduced) for measurement of biomarkers of interest (CRP, D-Dimer, and fibrinogen). Blood was sent for analysis, with no associated clinical information (i.e. blind sample). Demographic and clinical data were collected, including age, gender, stroke aetiology according to TOAST classification [18], stroke severity according to the National Institutes of Health Stroke Scale (NIHSS), and the presence of vascular risk factors, namely hypertension, diabetes mellitus (DM), dyslipidaemia, smoking history, hyperuricemia, obesity, atrial fibrillation (AF), and heart failure (HF).

At 48 hours, a new sample of peripheral blood was sent to the laboratory with no associated clinical information for S100β protein assay.

Functional evaluation

Functional assessment using the modified Rankin Scale (mRS) was performed at 48 hours (mRS48) and 12 weeks (mRS12) after stroke. The mRS score was dichotomized in "low functionality" (third-person dependence for daily life activities, corresponding to mRS 3, 4 and 5) and "good functionality" (greater independence in daily life activities, corresponding to mRS 0, 1 and 2) [5].

All patients underwent a standardised rehabilitation program over the course of 12 weeks in an inpatient setting. The treatment comprised 60 minutes of physiotherapy and 30 minutes of occupational therapy per day, as well as permanent supervision by rehabilitation nursing specialists.

Laboratory methods

CRP, D-Dimer, and fibrinogen were assayed using standardised procedures at the clinical centre, whereas S100β protein assays were completed using a specifically designed procedure (described below), which was conducted at “Biocant”—Biotechnology Innovation Center (Cantanhede, Portugal) due to the lack of standardised procedure at the hospital centre. CRP was measured with a latex immunoassay (Architect cSystem, Abbot Laboratories, USA), D-dimer with an automated latex enhanced immunoassay (Instrumentation Laboratory Company, Bedford, USA), and fibrinogen based on the Clauss method (Instrumentation Laboratory Company, Bedford, USA). All biomarkers were assayed using the manufacturer's standard reagents.

For S100β protein assays, samples were preserved at 5±3°C upon reception. Serum was separated on the same day at 1000G (approximately 2442 RPM) for 10 minutes at 20–25°C (using the Thermo Scientific CL30 centrifuge). The serum from each sample was distributed into 2 aliquots (one from the

top, Sample X.1 and one from the bottom, sample X.2) with a volume ranging from 1 mL to 1.5 mL, and frozen at -25°C. ELISA assays (BIOTEK, ELx808 and ELx50 models) were used to assess the concentration of S100β protein. All aliquots were ultra-frozen at about -80°C.

Statistical analysis

Variables with normal distribution (Shapiro-Wilk test) are summarised with mean and standard deviation and variables that do not follow a normal distribution are summarised by medians and interquartile range. Qualitative variables are described by absolute and relative frequencies; associations between qualitative variables were evaluated using Qui-square independence tests.

Multiple linear regression was used to evaluate the relationship between the NIHSS variable and biomarkers (fibrinogen, D-dimer, PCR, and S100β), controlling the effect of sociodemographic and clinical variables (gender, age, hypertension, DM, dyslipidaemia, hyperuricemia, obesity, AF, and HF).

Logistic regression was used to evaluate the relationship between the 12-week functionality measurement (mRS12) and biomarkers (fibrinogen, D-dimer, CRP, and S100β), controlling the effects of sociodemographic and clinical variables (gender, age, DM, dyslipidaemia, smoking, hyperuricemia, obesity, AF, and HF). The odds ratio (OR) is presented with the respective confidence interval of 95%.

The discriminative ability of variables to distinguish between individuals with "low functionality" and "good functionality " at 12 weeks was determined using the Receiver Operator Characteristic (ROC) methods.

Statistical analysis was performed using IBM SPSS Statistics version 22 (IBM Corp, Armonk, NY, USA), with significance set at 5%.

RESULTS

Study population

During the period of the study, a total of 556 patients were admitted to the stroke unit for acute ischaemic stroke. 166 patients meet the inclusion criteria and provided their informed consent to participate (reasons for exclusion are presented in supplementary materials). After enrolment, 10 patients had haemorrhagic transformation, 14 patients were lost to follow-up, and 11 patients were deceased during follow-up, leading to a final study population of 131 patients in which it was feasible to assess functionality at 12 weeks post-stroke.

Table 6.1 presents the demographic and clinical characteristics of the study population. Mean age in the final study population (n=131) was 68.8±11.9 years. Approximately half the study population (49.6%) was male. Mean NIHSS at admission was 14.7±6.6. According to the TOAST classification [18], the majority of strokes (51.9%) were of cardioembolic aetiology and 72.5% of patients underwent

fibrinolysis and/or thrombectomy [19]. At 48 hours, 13 patients (9.9%) presented good functionality (mRS between 0 and 2), which increased to 63 (48.1%) at 12 weeks.

Table 6.2 presents descriptive statistics for the biomarkers of interest as measured at the emergency department visit (PCR, D-dimer, and fibrinogen) or at 48 hours (S100β). Median levels of PCR, D-dimer, and fibrinogen were within the normal range at the emergency department visit, whereas S100β levels were substantially increased at 48 hours post-stroke (197.00 ng/dL).

Correlates of stroke severity

According to multiple linear regression analysis (**Table 6.3**), NIHSS scores on admission to the ER were significantly correlated with S100β (P=0.002) and fibrinogen (P=0.003) levels, but not with levels of D-Dimer and CRP. Additionally, there was also a significant positive correlation between female gender and NIHSS scores on admission (P=0.003). Other demographic and clinical variables were not significantly associated with NIHSS scores.

Correlates of functional outcome

Logistic regression analysis (**Table 6.4**) showed that S100β levels measured at 48 hours are significantly associated with mRS at 12 weeks (OR=1.003, 95%CI [1.001–1.004]; P<0.001). This association that was not seen for the remaining biomarkers of interest. Additionally, age (OR=1.047, 95%CI [1.003–1.093]; P=0.035) was also significantly associated with mRS at 12 weeks.

Predicting post-stroke functional outcome

It was possible to identify cut-off values of the biomarker S100β at 48 hours and NIHSS score at admission for classification of functionality at 12 weeks. ROC curve analysis for S100β and NIHSS scores are shown in **Figure 6.1**. The remaining biomarkers under study did not show statistically significant associations with mRS12.

The cut-off point from which patients were predicted to show low functionality at 12 weeks (i.e. mRS12 ≥3) according to the biomarker S100β was 140.5 ng/L, with sensitivity of 83.8%, specificity of 71.4%, and area under the curve (AUC) of 0.80 (P-value<0.001; AUC 95%CI: [0.722, 0.879]). The cut-off point for low-functionality at 12 weeks according NIHSS score at admission was 13.5, with sensitivity of 73.5%, specificity 58.7%, and AUC of 0.67 (P-value<0.001; AUC 95%CI: [0.722, 0.879]).

DISCUSSION

In this study, we assessed the potential of several biomarkers in predicting functional outcome after ischaemic stroke. S100β was highly correlated to functional outcome at both 48 hours and 12 weeks. To our knowledge this is the first study to establish S100β as a robust acute phase biomarker of medium to long term functional outcome after ischaemic stroke. Importantly, other biomarkers typically used to predict vital prognosis after ischaemic stroke (including CRP, D-Dimer, and fibrinogen) were not found to be strong predictors of functional outcome in this population.

The study sample showed sociodemographic characteristics and stroke aetiology comparable to those found in previous studies [1,20]. Occurrence of ischaemic injury is more frequent in patients with cerebrovascular risk factors. In this sample, however, most cerebrovascular risk factors were not significantly associated with NIHSS or functionality (as measured by mRS at 12 weeks). The exception was the association of age with worse functionally, which would be expected given that age is a well-established predictor of worse functional outcome.

Both the NIHSS and mRS are frequently used in the evaluation of neurological recovery and as primary endpoints in clinical studies of patients with stroke, and therefore constitute good measures of stroke severity, disability, and overall functional outcome [21]. In this study, the NIHSS mean score at admission of 14.72 and the mRS48 indicators (with good functionality in only 9.9% of cases) reflect the increased severity of functional deficits in the acute phase of stroke in our study population.

In our sample, there was also a remarkably high percentage of patients (72.5%) who underwent fibrinolysis and/or thrombectomy [19]. This finding is substantially above what would be expected for this region of the country (the Centre region), which might be explained by the fact that it is an observational study whose sample includes only patients admitted to a highly-differentiated stroke intervention unit.

Neuroplasticity is higher in the first 12 weeks after ischemic brain injury, which provides a relatively narrow window of action for patient recovery [22]. In this study, there was a significant increase in functionality during this period (48.1% of patients had a mRS indicator of good functionality at 12 weeks).

After ROC analysis, the cut-off point of 13.5 on the NIHSS scale was identified to predict functional classification. Other studies have identified cut-off values for NIHSS scores as predictors of 3-month functionality: NIHSS scores greater than 17 are associated with a higher probability of death or severe disability, and values below 6 are associated with a more favourable prognosis at 3 months [23]. Our results are in line with such studies, and contribute to further support the NIHSS scores as predictors of functionality.

Previous studies have also shown that high serum S100β levels are associated with worse post-stroke prognosis [11]. In our study population, for the assay of the S100β protein, a cut-off value of

140.5 ng/L was determined, with good AUC performance (0.80). These results support the hypothesis that S100β serum levels in the acute phase of stroke may have a predictive value in terms of functionality at 12 weeks post-stroke. Such findings are in agreement with previous studies that assessed the predictive value of S100β for other outcomes [10,11]. There was, however, no statistically significant association between other biomarkers (fibrinogen, D-dimers and CRP) and functionality, unlike what was found in previous studies assessing other types of outcomes [4–25]. Overall, this study contributes to establish the joint use NIHSS scores and S100β serum levels to more accurately predict patient functionality post-stroke.

The selection criteria defined for this study constitute a possible limitation, particularly in terms of age restrictions. Although the range of ages included in the study in relatively ample (18–85 years), patients >85 years were excluded; they remain, however, an important group in the context of stroke that should be evaluated in future studies. There is also a potential for selection bias that should be noted, since a majority of patients presenting with stroke in the study centre could not be included. This is mostly due to the specialised nature of this stroke unit to which patients with worse health status are referenced. Therefore, the study population might not be representative of the general Portuguese population. Our findings should be further explored in larger, preferably multicentre studies.

CONCLUSIONS

This study establishes S100β as a reliable predictor of functional outcome 12 weeks after stroke. Other biomarkers typically used to predict vital outcome (including CRP, D-Dimer, and fibrinogen) do not appear to be strongly associated with functional outcome. Additionally, S100β levels in peripheral blood measured in the acute phase of stroke (48 hours) appear to be a stronger predictor of functionality at 12 weeks than acute NIHSS scores.

Peripheral blood levels of S100β reflect the severity of stroke and predict functional prognosis, with levels ≥140.5 ng/L indicating low functionality at 12 weeks. The clinical utility of S100β as predictor of functional recovery after-stroke should be emphasised in clinical practice, tough large-scale studies with longer follow-up periods should be conducted to further validate the use of this biomarker.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

FUNDING SOURCE

There were no external sources of funding.

ACKNOWLEDGEMENTS

The authors thank Graça Fernandes (Stroke Unit, Centro Hospitalar Universitário de Coimbra) for providing nursing care throughout the study; Marisa Loureiro (Laboratory of Biostatistics and Medical Informatics, Faculty of Medicine of the University of Coimbra) for providing assistance during statistical analysis; and Tiago Campos (ARC Publishing) for providing editorial assistance.

AUTHOR CONTRIBUTIONS

JPB, JSF and JP designed the study; JPB, JC, SO, collected the data; JPB, JSF, LC, GC contributed to data analysis and interpretation, JPB, SO, JSF drafted the manuscript; AGF, JP, JPB , JSF conducted critical analysis of the contents of the manuscript; and all authors reviewed and approved the final manuscript.

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TABLES

Table 6.1 – Demographic and clinical characteristics of the study population.

Characteristic	Study population (n=131)
Gender, n (%)	
Male	65 (49.6)
Female	66 (50.4)
Age, yrs	
Mean ± SD	68.8±11.9
Range (min–max)	32–85
Comorbidities/lifestyle factors, n (%)	
Hypertension	91 (69.5)
Diabetes Mellitus	38 (29.0)
Dyslipidaemia	59 (45.0)
Hyperuricemia	16 (12.2)
Atrial fibrillation	59 (45.0)
Heart Failure	27 (20.6)
Obesity	25 (19.1)
Smoking	16 (12.2)
Stroke assessments, n (%)	
TOAST (cardioembolic)	68 (51.9)
Fibrinolysis/Thrombectomy	95 (72.5)
mRS48 (score 0–2)	13 (9.9)
mRS12 (score 0–2)	63 (48.1)
NIHSS, mean±SD	14.72±6.56

mRS12 = Modified Rankin Scale score at 12 week; mRS48 = Modified Rankin Scale score at 48 hours; NIHSS = National Institutes of Health Stroke Scale; SD = Standard deviation; TOAST = Trial of Org 10172 in Acute Stroke Treatment.

Table 6.2 – Descriptive statistics for levels of biomarkers of interest at admission (CRP, D-dimer, and fibrinogen) or at 48 hours after admission (S100β).

Variable	n	Mean (SD)	Median (IQR)	Minimum	Maximum
CRP (mg/dl)	131	1.61±3.47	0.49 (1.00)	0.02	20.40
D-dimer (µg/l)	131	1.47±2.22	0.82 (1.41)	0.00	18.30
Fibrinogen (g/l)	131	2.91±1.27	2.70 (1.10)	0.00	11.40
S100β (ng/L)	131	439.76±562.03	197.00 (462.00)	38.00	3254.00

CRP = C-reactive protein; IQR = Interquartile range; SD = Standard deviation; S100β = S100β protein

Table 6.3 – Multiple linear regression to determine the relationship between patient characteristics/biomarkers and NIHSS score at admission.

	Multiple linear regression (n=131)	
Variables	**β**	***P*-value**
Gender (female)	**3.559**	**0.003**
Age	- 0.017	0.804
Hypertension	- 0.729	0.564
Diabetes Mellitus	0.257	0.838
Dyslipidaemia	- 0.355	0.755
Obesity	- 1.054	0.464
Atrial Fibrillation	- 0.591	0.601
Heart Failure	0.700	0.617
S100β	**0.003**	**0.002**
D-dimer	0.065	0.802
Fibrinogen	**1.473**	**0.003**
CRP	- 0.035	0.840

The adjusted coefficient of determination (R^2) is 0.162 ($p < 0.001$).
P-values adjusted for: gender, age, hypertension, diabetes mellitus, dyslipidaemia, atrial fibrillation, and heart failure.
CRP = C-reactive protein; NIHSS = National Institutes of Health Stroke Scale; S100β = S100β protein

Table 6.4 – Logistic regression to determine the relationship between patient characteristics/biomarkers and mRS scores at 12 weeks.

Variables	Logistic regression (n=131)		
	Odds Ratio	**95% CI**	***P*-value**
Gender (female)	2.205	0.839 – 5.792	0.109
Age	**1.047**	**1.003 – 1.093**	**0.035**
Hypertension	0.778	0.282 – 2.147	0.628
Diabetes Mellitus	2.516	0.900 – 7.036	0.079
Dyslipidaemia	0.513	0.204 – 1.295	0.158
Obesity	1.398	0.448 – 4.360	0.564
Atrial Fibrillation	0.754	0.295 – 1.925	0.555
Heart Failure	0.638	0.183 – 2.231	0.482
S100β	**1.003**	**1.001 – 1.004**	**<0.001**
D-dimers	1.142	0.931 – 1.401	0.204
Fibrinogen	1.686	1.084 – 2.621	0.020
CRP	0.883	0.730 – 1.068	0.198

R^2 Nagelkerke = 46.1%, $P<0.001$.
P-value adjusted for gender, age, hypertension, diabetes mellitus, dyslipidaemia, smoking, hyperuricemia, obesity, atrial fibrillation, and heart failure.
CRP = C-reactive protein; mRS = modified Rankin Scale; S100β = S100β protein

FIGURES

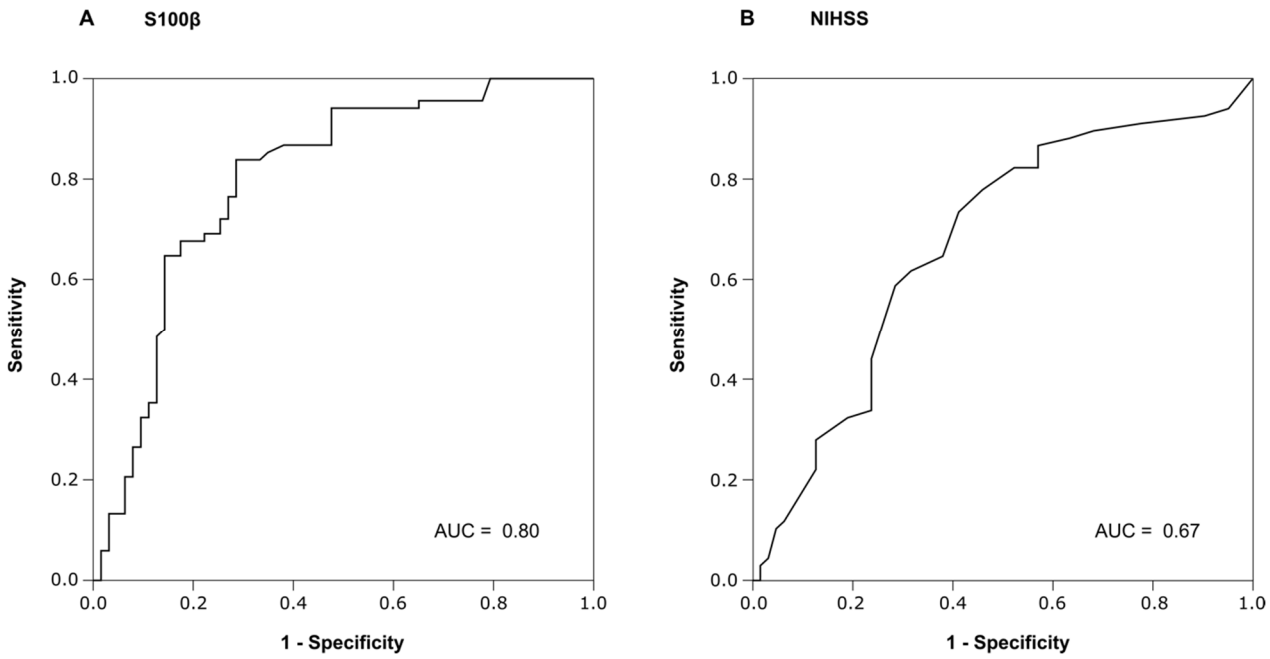

Figure 6.1 – ROC curves testing the performance of S100β (curve A) and NIHSS (curve B) in predicting functionality (mRS12w) at 12 weeks post-stroke.

AUC = Area under the curve; mRS12w = modified Rankin Scale at 12 weeks; NIHSS = National Institutes of Health Stroke Scale; ROC = Receiver Operating Characteristic

SUPPLEMENTARY MATERIAL

Supplementary table 6.1 – Reasons for exclusion from the study.

Exclusion criteria	No of patients
No CT at admission	25
Stroke >3 hours prior to admission	55
Premorbid mRS>2	45
Active infection	35
Renal insufficiency	25
Active malignancy	36
No blood sample within 48 hours of admission	45
Premorbid neurocognitive pathology	50
Symptom onset >6 hours	28
Recent surgery	24
Coma	22

CHAPTER 7

NEUROIMAGING, SERUM BIOMARKERS, AND PATIENT CHARACTERISTICS AS PREDICTORS OF UPPER LIMB FUNCTIONING

Published as:

Neuroimaging, serum biomarkers, and patient characteristics as predictors of upper limb functioning 12 weeks after acute stroke: an observational, prospective study

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Top Stroke Rehabil. 2018 Sep 13:1-7. DOI: 10.1080/10749357.2018.1517491.

Title: Neuroimaging, serum biomarkers, and patient characteristics as predictors of upper limb functioning 12 weeks after acute stroke: an observational, prospective study

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ABSTRACT

Objective: To evaluate the potential of neuroimaging, serum biomarkers, stroke aetiology, and clinical characteristics as predictors of upper limb functioning 12 weeks after stroke.

Methods: This was a prospective, observational study of patients (18–85 years-old) hospitalised due to acute ischaemic stroke in the territory of the middle cerebral artery. Patients were hospitalised at a stroke rehabilitation centre, where they underwent a standardised rehabilitation program. Clinical, imagiology, laboratory (biomarkers: C-reactive protein, D-dimer, and fibrinogen, and S100 calcium binding protein β [S100β]), and functionality assessments were conducted 4 different times: within 24 hours, and at 48 hours, 3 weeks, and 12 weeks after acute stroke.

Results: Upper limb functioning at 12 weeks was significantly associated with Alberta Stroke Program Early CT Score (ASPECTS) score (OR:2.012 [CI:1.349–3.000]; P=0.001) and S100β protein levels (OR:0.997 [CI:0.994–0.999]; P=0.007). Advanced age was associated with poor upper limb functioning. S100β protein levels <140.5 ng/L at 48 hours and ASPECTS scores ≥7.5 within 24 hours of admission predicted good hand functioning at 12 weeks. Upper limb functioning and general functioning were significantly correlated (P<0.001), with strong negative correlations (all correlation coefficients ≤-0.586) for all comparisons.

Conclusion: ASPECTS score ≥8 within 24 hours and S100β protein <140.5 ng/L at 48 hours predict better upper limb functioning, while advanced age predicts worse upper limb functioning 12 weeks after stroke.

Keywords: Stroke; Biomarkers; S100β; ASPECTS; Rehabilitation; Upper Limb; Hand; Functionality

BACKGROUND

Stroke is the main cause of disability in western societies in people over 50 years old (1,2). A substantial portion of patients surviving stroke suffer permanent disability (15–30%) and approximately 20% of patients require inpatient care during the first 3 months post-stroke (3). These first 12 weeks constitute a window of opportunity of particular interest in terms of patient recovery, since neuroplasticity is higher during the first 12 weeks post-stroke (4) and, therefore, most of the gains are expected to occur within this period.

Currently, computed tomography (CT) of the head is one of the most widely used diagnostic tools for the assessment of stroke patients during the acute phase. The interpretation of CT scan results is vastly improved by the use of standardised assessment scales. The Alberta Stroke Program Early CT Score (ASPECTS) evaluates the topography of the brain lesion based on the CT scan image and classifies the level of brain damage on a standardised scale (5–7).

In addition to the CT data, numerous biomarkers have also been explored as predictors of vital and functional outcome in the context of acute stroke. C-reactive protein (CRP), fibrinogen, D-dimers and, S100 calcium binding protein β (S100β) are among the most widely studied and established markers of structural brain lesion, disability, and mortality in the context of acute stroke (8,9). Several studies report significantly increased S100β protein levels in peripheral blood 12 hours after brain lesion (10,11), which peak between the second and third days after the lesion occurs (10,11). Additionally, previous studies have also established that S100β protein levels >0.027 ng/mL in peripheral blood lead to changes in the permeability of the blood–brain barrier (8,10).

The sub-type of ischaemic stroke itself has been shown to predict different outcomes for the patient. Approximately 25% of ischaemic strokes have cardioembolic aetiology (12), which is associated with overall worse prognosis. Patients with cardioembolic stroke have worse clinical and functional prognosis, with higher intra-hospital mortality during the acute phase and worse functioning at discharge (13). Therefore, the type of stroke endured by the patient is an important factor that should be weighted when establishing models to predict functioning level after stroke.

Upper limb impairment represents an important portion of disability caused by stroke. In the acute phase, approximately 70% of stroke patients show hemiparesis with brachial predominance (3). In clinical practice, several instruments are used to quantify functional capacity after stroke (14). The Stroke Upper Limb Capacity Scale (SULCS) is a unidimensional, hierarchical, and consistent scale that evaluates the functional capacity of the upper limb (15–17). The scale includes items that evaluate basic hand functioning (activities that require little or no hand function) and items that evaluate more demanding hand functioning (activities that require good distal function) (15–17).

When considering the overall disability, and specifically, upper limb disability resulting from stroke there is a clear need for improvement of treatment and rehabilitation programs for stroke patients

(18–21). These types of programs can potentially be informed by recognised markers of functional prognosis. This study aims to evaluate the potential of neuroimaging, serum biomarkers, stroke aetiology, and clinical characteristics as predictors of the upper limb functioning 12 weeks after stroke. Additionally, the study also aims to assess the relationship between overall functionality and upper limb functionality.

METHODS

Study design and population

This is a prospective, observational study of patients hospitalised due to acute stroke in a tertiary care hospital in Portugal (Centro Hospitalar e Universitário de Coimbra) from April 2015 to April 2016.

Patients were eligible to participate in the study if they had clinical and imagiology assessments indicative of ischaemic stroke in the territory of the middle cerebral artery and were 18 to 85 years-old. Patients were excluded from the study if they fulfilled at least one of the following criteria: (a) presence of haemorrhagic transformation; (b) symptoms of acute stroke >3 hours before admission; (c) presence of neurological, inflammatory, or neoplastic diseases; (D) no peripheral blood drawn; and (e) no head CT done during index hospitalisation.

During the period of the study, patients were hospitalised at a stroke rehabilitation centre, where they underwent a standardised rehabilitation program (according to routine clinical practice). The rehabilitation program included 60 minutes of physical therapy and 30 minutes of occupational therapy daily, as well as permanent supervision by nursing staff specialised in stroke rehabilitation.

The study received favorable opinion from the Scientific Council of the Ethics Committee of the Faculty of Medicine of the University of Coimbra (reference letter 104-CE-2014). All patients or their legal representatives provided their written informed consent prior to study enrolment.

This manuscript conforms to the requirements laid out in the STROBE Guidelines.

Assessments

Patients were evaluated at 4 different times: within 24 hours of hospitalisation, at 48 hours, at 3 weeks, and at 12 weeks after acute stroke.

Within the first 24 hours after hospital admission, patients underwent a head CT, which was evaluated with ASPECTS scoring. A peripheral blood sample was collected before any fibrinolytic or antithrombotic therapy was instituted, to measure the levels of the following biomarkers: C-reactive protein, D-dimer, and fibrinogen. After observation by a neurologist, clinical and demographic data were collected, including: age, gender, stroke sub-type according Trial of ORG 10172 in Acute Stroke

Treatment (TOAST) classification, and the presence of vascular risk factors, namely hypertension, diabetes mellitus, dyslipidaemia, obesity, atrial fibrillation, heart failure, and smoking.

At 48 (±12) hours after acute stroke, a new peripheral blood sample was collected to measure S100β protein. At this time, the general functional capacity of patients was assessed using the modified Rankin Scale (mRS) and the upper limb functional capacity was assessed using SULCS.

At 3 and 12 weeks after acute stroke, functional capacity was again assessed using mRS and SULCS.

All mRS and SULCS assessments were conducted by the same physician (first author).

Assessment scales

SULCS is a stroke-specify, easy-to-use scale that can be completed in approximately 6 minutes and is based on the execution of 10 functional tasks related to the activities of daily living of patients. The scale is composed of 3 items evaluating upper limb proximal function, 4 items evaluating basic hand function, and 3 items evaluating advanced hand functioning (16,22). Tasks are unidimensional and ordered with increasing degree of difficulty. Scoring is dichotomic (0=not possible to complete the task; 1=task completed properly), with higher scores indicating higher degree of upper limb functioning (16,22). The results can be categorised as: no hand functioning (scores 0-3), basic hand functioning (scores 4-7), and good hand functioning (scores 7-10) (16,22).

The ASPECTS scale is aimed at providing a quantitative measure of brain lesion, based on the topographic analyses (5,6). The ASPECTS score is obtained by dividing the territory of the middle cerebral artery into 10 regions of interest (M1-M6, I = Insular ribbon, IC = Internal capsule, L = Lenticular nucleus, and C = Caudate nucleus) (5,6). The areas of the middle cerebral artery are considered based on their functional relevance instead of brain lesion extension (5,6). To calculate the final score, 1 point is subtracted from 10 for each of the regions of interest that show signs of brain lesion (5,6), thus lower scores are indicative of more extensive brain lesions.

Clinical laboratory methods

Peripheral blood samples collected during the study were sent for analysis without any identifying or clinical information (i.e. blind sample). C-reactive protein levels were assessed with a latex immunoassay (Architectc System, Abbot Laboratories, USA), D-dimer with an automated latex enhanced immunoassay (Instrumentation Laboratory Company - Bedford, USA), and fibrinogen based on the Claussmethod (Instrumentation Laboratory Company - Bedford, USA). All the above-mentioned biomarkers were assayed using the standard procedures implemented at the study site, using the manufacturer's instructions and standard reagents. Essays were conducted at certified laboratories at the study centre (UK NEQAS certification).

S100β protein levels were assessed using a specific laboratory methodology, since this biomarker is not routinely assessed at the study site. Assessments were conducted at a specialized site, Biocant—Biotechnology Innovation Center (Cantanhede, Portugal) following standardised and validated procedures. This is a certified laboratory (EN ISO/IEC 17025:2005 certification). Samples were preserved at 5±3ºC. During the day of reception, serum was separated at 1000g (approximately 2443 RPM) for 10 minutes at 20–25ºC (using a Thermoscientific CL30 centrifuge). Serum from each sample was divided into 2 aliquots (1 aliquot from the top, sample X.1, and 1 aliquot from the bottom, sample X.2), both with volume 1.0–1.5 mL; aliquots were stored at -25ºC. S100β protein levels were quantified using ELISA assays (BIOTEK, ELx808, and ELx50 models). All samples were frozen at -80ºC for storage.

Statistical methods

Qualitative variables are described by their absolute and relative frequencies, while quantitative variables are described by their median, first and third quartile, minimum and maximum. The normality of quantitative variables was assessed through the Shapiro-Wilk test. Univariate analysis was conducted using Mann-Whitney or Chi-square tests as appropriate.

For the purposes of functionality assessment, the results of mRS assessments were dichotomised into “Low Functioning” (scores of 3 to 5) and “Good Functioning” (scores of 0 to 2) (9). In order to assess the impact of stroke aetiology on upper limb functioning, we categorised aetiology as cardioembolic and non-cardioembolic since the distribution of patients in the other TOAST categories was not sufficient to provide adequate statistical power. This type of categorisation was selected because previous studies indicate that patients with cardioembolic stroke have worse prognosis compared to other aetiologies (23).

The results of SULCS assessments are typically presented in the following three categories: no hand functioning (score 0–3), basic hand function (score 4–7), and good hand functioning (score 8–10) (15). In this study, however, for the purpose of analyses we dichotomised the scale into no hand functioning (score 0–3) or hand functioning (score 4–10), because the data was not sufficiently distributed to provide the required statistical power with 3 categories.

Correlations between mRS and SULCS scores at both 3 weeks and 12 weeks were evaluated using the Spearman correlation coefficient.

Receiver Operator Characteristic (ROC) analyses were conducted to evaluate the discriminative capacity of quantitative variables (ASPECTS score and S100β protein levels) to distinguish between individuals with “No hand functioning” and “Hand Functioning” according to SULCS scores.

A logistic regression model was applied to assess the effect of biomarkers and baseline variables on the probability of “Hand Functioning” at 12 weeks. Variables with $P<0.05$ in univariate analysis

were considered in the logistic regression model. Age and gender were included in the model as control variables, irrespective of univariate analysis results.

Statistical analyses were performed using IBM SPSS Statistics version 22 (IBM Corp, Armonk, NY, USA), with level of significance of 5%.

RESULTS

Study population

A total of 556 patients were admitted to the centre with acute ischaemic stroke during the study period and 166 of those were eligible to participate in the study. However, 10 patients were excluded due to haemorrhagic transformation, 14 patients were lost to follow-up, and 11 patients died during the period of the study.

Approximately half the participants were women (n=66; 50.4%), and mean age was 68.8±11.9 years. Comorbidities were frequent in this population: hypertension (69.5%), dyslipidaemia (45.0%), atrial fibrillation (45.0%), diabetes (29.0%), heart failure (20.6%), obesity (19.1%).

Stroke aetiologies (TOAST classification) were distributed as follows: cardioembolic (51.9%), other determined aetiology (19.1%), undetermined aetiology (15.3%), small-vessel occlusion (9.2%), and large-artery atherosclerosis (4.6%).

Biomarker measurements at admission revealed median levels of C-reactive protein (0.49 mg/dL [IQR: 1.00]), D-Dimer (0.82 μg/L [IQR: 1.41]), and fibrinogen g/dL (2.70 [IQR: 1.10]) within the normal range. Importantly, median S100β levels were increased at 48 hours (197.00±462.00 ng/L). Patients showed a median ASPECTS score within the first 24 hours of admission of 8 (IQR: 4), indicative of involvement of few brain areas for most participants.

Upper limb functioning and general functioning

At 3 weeks, 37.4% of participants showed good general functioning (mRS scores 0–2), raising to 48.1% at 12 weeks. As for upper limb functioning, 48.1% of participants showed hand functioning (SULCS 4–10) at 3 weeks and 55.7% of participants at 12 weeks, according to SULCS scores. Men and young patients showed significantly better general and upper limb functioning (**Table 7.1**). In terms of comorbidities and lifestyle factors, only the presence of diabetes or smoking history showed significant association with general functioning. The cardioembolic, large-artery atherosclerosis, and small-vessel occlusion subtypes of ischaemic stroke tended to be associated with worse upper limb functioning, but did not reach statistical significance.

SULCS and mRS scores were significantly correlated (P<0.001), with strong negative correlations (all correlation coefficients ≤-0.586) for all comparisons (**Table 7.2**). SULCS scores in the

acute phase (48 hours) showed strong correlations with mRS scores in the short- to medium-term at both 3 weeks and 12 weeks after stroke (correlation coefficients ≤-0.635, $P<0.001$). Additionally, SULCS scores at 48 hours were also strongly correlated with SULCS scores at 3 weeks and 12 weeks (correlation coefficient of 0.717, $P<0.001$).

Predictors of upper limb functioning

In multivariate analysis, the characteristics that were significantly associated with hand functioning at 12 weeks were the ASPECTS score (OR: 1.1696 [CI: 1.261–2.281]) and S100β protein levels at 48 hours (OR: 0.998 [CI: 0.997–1.000]) (**Table 7.3**), with sensitivity of 83.6% and specificity of 71.0%, correctly explaining 77.9% of cases.

In sensitivity analysis, the non-significant variables were consecutively removed by decreasing order of *P*-value; then, variables with very small β (-0.01<β<0 or 0>β>0.01) were also removed from the multivariate model. This lead to a final multivariate model with 2 significant variables: ASPECTS score (OR: 2.012 [CI: 1.552–2.609]) and age >65 years (OR: 0.246 [CI: 0.086–0.705]), with a sensitivity of 86.3% and specificity of 62.1%, correctly explaining 75.6% of cases.

It was feasible to identify cut-off values for S100β protein levels and ASPECTS scores to classify upper limb functioning at 12 weeks after stroke. S100β protein levels <140.5 ng/L at 48 hours after admission are predictors of hand functioning at 12 weeks, with 68.5% sensitivity, 89.7% specificity, and 0.839 (CI: 0.769–0.908) area under the curve (AUC). ASPECTS scores ≥7.5 within 24 hours of admission are predictors of hand functioning at 12 weeks, with 74.0% sensitivity, 74.1% specificity, and 0.812 (CI: 0.739–0.886) AUC (see **Figure 7.1** for ROC curves).

DISCUSSION

This study assessed the potential of neuroimaging, selected serum biomarkers, and clinical characteristics in predicting upper limb functioning after ischaemic stroke in the territory of the middle cerebral artery. S100β protein levels, ASPECTS scores, and age were significantly associated with upper limb functioning 12 weeks after stroke. Other markers typically used for vital prognosis after stroke (including C-reactive protein, D-Dimers, and fibrinogen) were not significantly associated with upper limb functioning, which emphasises the need to specifically assess upper limb functioning, since it does not appear to be accurately captured by classical vital prognosis markers.

Patients with history of stroke rate upper limb functioning as a highly relevant factor for their overall quality of life (24), given the high impact of the execution of activities of daily living (25,26). Previous studies suggest, however, that only 25–45% recover full functionality of the upper limb 2 to 3 years after acute stroke (24). Up to 45% of patients maintain low upper limb functionality even 4 years after the acute stroke episode (24), which results in substantial functional and quality of life impairment.

Thus, given the relevance of upper limb functioning for overall patient recovery and quality of life, it is very important to establish easy-to-use, acute predictors of upper limb functioning that can inform prognosis and guide treatment/rehabilitation programs. In the increasingly prevalent context of resource-constrained healthcare systems, it is important to establish early, individualised rehabilitation programs aimed at improving patient outcomes and which, consequently, can reduce resource utilisation in later stages.

Overall functional capacity was highly correlated with upper limb functionality in this population, both in the short term (3 weeks) and medium term (12 weeks). This type of correlation was expected, since upper limb functionality is a constituent part of overall functionality measured by mRS. Although the correlations between the two scales were high, it is important to ensure patients receive specific upper limb assessments when establishing their treatment and rehabilitation programs. Upper limb functioning, and particularly, hand functioning is crucial for the execution of activities of daily living and for patient quality of life after stroke, therefore it should be considered when managing these patients.

In this study, most patients had stroke of cardioembolic aetiology, which would be expected based on incidence estimates for the different aetiologies (1). In this population, patients with cardioembolic stroke tended to show higher risk of having no hand functioning at 12 weeks. Although our findings did not reach statistical significance, the trend is in accordance with previous studies that suggested worse neuromotor function following cardioembolic stroke (23).

Head CT is one of the most widely used imagiology tools to evaluate patients with acute stroke and, therefore, we included this type of data when developing a predictive model of upper limb functioning after stroke. Previous studies established that patients with ASPECTS score 8–10 shortly after acute stroke show higher functional capacity (mRS $\leq$3), while patients with low ASPECTS score are unlikely to regain functional independency (5). A study by Menon et al. found that patients with ASPECTS $\leq$7 points had a low probability of regaining functional independency. While patients with ASPECTS 6–10 had a 50% probability of regaining full independency, those with ASPECTS 0–3 had only a 15% probability of achieving full independency (27). Our findings follow the same trend seen in those studies but applied to the context of upper limb functionality. ASPECTS scores within the first 24 hours of admission showed a strong positive association with upper limb functionality, indicating that the lower the number of brain regions affected, the higher the number of upper limb functions the patient will be able to execute at 12 weeks. The cut-off for hand functioning at 12 weeks found in this population was $\geq$7.5 points, which is consistent with previous studies that evaluated overall functionality (5,27). The results indicate that ASPECTS could play a significant role in the care of stroke patients in routine clinical practice, as it is highly predictive of patient functioning in the medium to long-term.

High S100β protein levels were previously associated with worse overall prognosis after stroke in several studies (28,29). Here, higher S100β protein levels were, in fact, strongly associated with poor upper limb functioning, with a cut-off of 140.5 ng/L. These findings are in agreement with previous reports (28,29), supporting the hypothesis that serum level of S100β protein in the acute phase predicts patient functionality after stroke, although in this case, specifically, upper limb functionality. Interestingly, other peripheral blood biomarkers (C-reactive protein, D-dimers, and fibrinogen) were not significantly associated with upper limb functionality, contrary to previous studies (9,30). It is important to note, however, that the effect of S100β protein levels in the multivariate model was very small. A simplified multivariate model without S100β and non-significant variables showed a sensibility of 86.3% (compared to 83.6% for the complete model with all variables including S100β) and a specificity of 62.1% (compared to 71.0%). While the simplified model presents substantially lower specificity (9 percentage points lower), given the significant cost and accessibility issues of S100β assays, the value of S100β in routine clinical practice could be substantially impacted.

This study has limitations that should be noted. The study population was relatively heterogeneous, particularly in terms of age. On one hand this can be an asset since it provides a more accurate picture of the overall stroke population, but on the other hand it can also introduce some limitations in identifying relevant trends in different age strata. Additionally, the study was conducted on a single, highly-specialised stroke treatment centre. Due to the highly specialised nature this centre receives highly debilitated patients, which can introduce a potential for selection bias, since a large proportion of patients could not be enrolled in the study. Therefore, further multicentre studies would be of interest to improve representativeness of the general population. The exclusion criteria applied could also lead to an underrepresentation of patients with larger lesions and, thus, lead to the underrepresentation of patients with lower functioning in the analyses.

CONCLUSIONS

This study establishes a panel of neuroimaging, serum, and clinical markers as predictors of upper limb functioning 12 weeks after stroke. ASPECTS score ≥8 within 24 hours of hospital admission and serum levels of S100β protein <140.5 ng/L at 48 hours after hospital admission predict better upper limb functioning 12 weeks after stroke. Conversely, advanced age is significantly associated with worse upper limb functioning 12 weeks after stroke.

Upper limb functioning measured in the acute phase of stroke (48 hours) is strongly correlated with overall functioning and upper limb functioning after stroke both in the short- and medium-term (3 and 12 weeks). These findings suggest that SULCS in the acute phase of stroke can provide valuable insight for medium-term functional recovery, which warrants investigation in future studies.

When considering the impact of upper limb functioning in the execution of activities of daily living and overall patient quality of life, these results highlight the importance of assessing upper limb functioning in stroke patients and provide valuable insights to support the design of treatment and rehabilitation programs for stroke patients.

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FIGURES

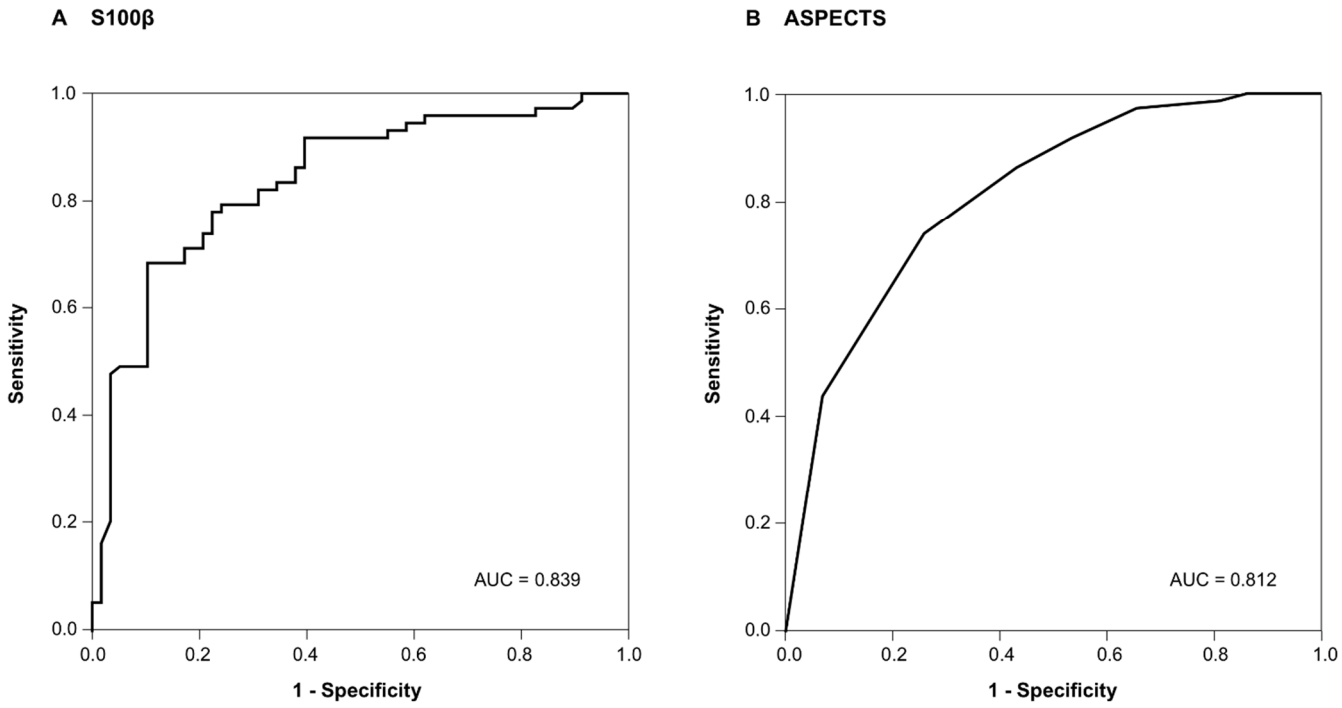

Figure 7.1 – ROC curves assessing the performance of (A) S100β at 48 hours and (B) ASPECTS score within 24 hours in predicting upper limb functioning (measured by SULCS) at 12 weeks after stroke.

ASPECTS = Alberta Stroke Program Early CT Score; AUC = Area under the curve; ROC = Receiver Operating Characteristic

TABLES

Table 7.1 – Upper limb and general functioning in the study population 12 weeks after stroke, according to patient characteristics.

	SULCS			mRS		
	Hand functioning	**No hand functioning**	**p-value**	**Good functioning**	**Low functioning**	**p-value**
Total population, n (%)	73 (55.7)	58 (44.3)	–	63 (48.1)	68 (51.9)	–
Age (yrs), n (%)						
18–65 (n=45)	31 (42.5)	14 (24.1)	0.028	31 (49.2)	14 (20.6)	0.001
≥65 (n=83)	42 (57.5)	44 (75.9)		32 (50.8)	54 (79.4)	
Gender, n (%)						
Male (n=65)	44 (60.3)	21 (36.3)	0.006	40 (61.5)	25 (38.5)	0.002
Female (n=66)	29 (39.7)	37 (63.8)		23 (34.8)	43 (65.2)	
Comorbidities/lifestyle factors, n (%)						
Atrial fibrillation (n=59)	36 (49.3)	23 (39.7)	0.270	29 (49.2)	30 (50.8)	0.826
Dyslipidaemia (n=59)	36 (49.3)	23 (39.7)	0.270	32 (54.2)	27 (45.8)	0.203
Hypertension (n=91)	53 (72.6)	38 (65.5)	0.382	43 (47.3)	48 (52.7)	0.772
Diabetes (n=38)	19 (26.0)	19 (32.8)	0.399	13 (34.2)	25 (65.8)	0.042
Hyperuricemia (n=16)	6 (8.2)	10 (17.2)	0.117	4 (25.0)	12 (75.0)	0.048
Obesity (n=25)	15 (20.5)	10 (17.2)	0.632	13 (52.0)	12 (48.0)	0.664
Hearth Failure (n=27)	14 (19.2)	13 (22.4)	0.649	14 (51.9)	13 (48.1)	0.661
Smoking (n=16)	12 (16.4)	4 (6.9)	0.098	12 (750)	4 (25.0)	0.021
TOAST subtypes, n (%)						
Cardioembolic (n=68)	36 (49.3)	32 (55.2)		30 (44.1)	38 (55.9)	
Large-artery atherosclerosis (n=6)	2 (2.7)	4 (6.9)		1 (167)	5 (83.3)	
Small-vessel occlusion (n=12)	6 (8.2)	6 (10.3)	0.369	4 (33.3)	8 (66.7)	0.084
Other determined aetiology (n=25)	18 (24.7)	7 (12.1)		17 (68.0)	8 (32.0)	
Undetermined aetiology (n=20)	11 (15.1)	9 (15.5)		11 (55.0)	9 (45.0)	
Biomarkers						
S100β	107.0 (70.0, 231.5)	543.0 (282.5, 943)	< 0.001	93.0 (70.0, 233.0)	429.0 (181.8 847.5)	< 0.001
C-reactive protein	0.49 (0.19, 1.30)	0.46 (0.18, 1.11)	0.718	0.46 (0.19, 1.61)	0.52 (0.21, 1.07)	0.809
Fibrinogen	2.70 (2.15, 3.10)	3.05 (2.50, 3.90)	0.001	2.7 (2.2, 3.1)	2.9 (2.4, 3.8)	0.014
D-Dimer	0.69 (0.29, 1.78)	0.91 (0.46, 1.9(	0.075	0.82 (0.28, 1.8	0.82 (0.45, 1.6(	0.451
ASPECTS score	8.0 (7.0, 9.0)	6.0 (4.0, 8.0)	< 0.001	8.0 (7.0, 9.0)	7.0 (4.3, 8.0)	< 0.001

Data presented as median (first quartile, third quartile), except when otherwise indicated.
SULCS categorisation: Hand function defined as scores 4–10 and No hand function defined as scores 0–3.
mRS categorisation: Good functioning defined as scores 0–2 and Low functioning defined as scores 3–5.
mRS = Modified Rankin Scale; SULCS = Stroke Upper Limb Capacity Scale; TOAST = trial of ORG 10172 in acute stroke treatment.

Table 7.2 – Correlation matrix for mRS and SULCS scores at 3 weeks and 12 weeks.

	SULCS 48 hours	**SULCS 3 weeks**	**SULCS 12 weeks**	**mRS 48 hours**	**mRS 3 weeks**	**mRS 12 weeks**
SULCS 48 hours	—	0.784**	0.717**	-0.697**	-0.698**	-0.635**
SULCS 3 weeks	0.784**	—	0.885**	-0.586**	-0.830**	-0.755**
SULCS 12 weeks	0.717**	0.885**	—	-0.574**	-0.797**	-0.849**

mRS = Modified Rankin Scale; SULCS = Stroke Upper Limb Capacity Scale

***P*<0.001

Table 7.3 – Logistic regression assessing the relationship between patient characteristics and hand functioning (according to SULCS scores) at 12 weeks.

Independent variables	β	OR	95% CI	*P*-value
ASPECTS (24 hours)	0.528	1.696	1.261 – 2.281	< 0.001
S100β (48 hours)	- 0.002	0.998	0.997 – 1.000	0.043
Age (> 65 yrs)	- 1.079	0.340	0.115 – 1.009	0.052
Gender (Male)	0.852	2.344	0.933 – 5.888	0.070

The logistic regression model reached statistical significance (χ^2 (4)= 61.951; *P*<0.001). Model explains 50.5% (Nagelkerke R^2) of variability in upper limb functioning and classifies 77.9% of cases correctly.

95% CI = 95% Confidence interval; ASPECTS = Alberta Stroke Program Early CT Score; β = regression coefficient; OR = Adjusted odds ratio; SULCS = Stroke Upper Limb Capacity Scale.

CHAPTER 8

FUNCTIONAL RECOVERY IN THE FIRST 6 MONTHS AFTER ACUTE ISCHAEMIC STROKE

Published as:

Assessing functional recovery in the first 6 months after acute ischaemic stroke: a prospective, observational study

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Eur J Phys Rehabil Med. 2019 Feb;55(1):1-7. DOI: 10.23736/S1973-9087.18.05161-4.

Title: Assessing functional recovery in the first 6 months after acute ischaemic stroke: a prospective, observational study

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ABSTRACT

Background: Stroke is a major cause of short-term functional impairment, but the recovery timeframes are not well-established.

Aim: This study aims to evaluate the progression of functional recovery during the first 24 weeks after acute ischaemic stroke, to determine the timeframes for (a) motor, (b) cognitive, and (c) overall recovery.

Design: Prospective observational study

Setting: Tertiary care centre; 12-week inpatient period, followed by 12-week outpatient period.

Population: A group of 131 patients with acute stroke in the territory of the middle cerebral artery with age 18–85 years-old.

Methods: Patients received treatment according to routine clinical practice and underwent a closely-controlled rehabilitation program for 24 weeks. Functionality assessments were conducted at 48 hours, 3 weeks, 12 weeks, and 24 weeks after acute stroke and included the modified Rankin Scale (mRS), the Functional Independence Measure (FIM), and the Stroke Upper Limb Capacity Scale (SULCS).

Results: Over the study period, patient functionality improved significantly ($P<0.001$) as measured by all scales. Assessment scores improved significantly from 48 hours to 3 weeks for all scales; the same occurred from 3 weeks to 12 weeks, except for C-FIM. From 12 weeks to 24 weeks, there were no statistically significant functional improvements for any scale. In comparative terms, cognitive impairment was less severe than motor disability in the acute phase. C-FIM scores at 48 hours were significantly higher than M-FIM and mRS scores. Upper limb functioning measured by SULCS, showed an intermediate degree of disability compared to the C-FIM, M-FIM, and mRS.

Conclusions: Functional recovery occurs at least until 24 weeks after acute stroke, but most the of the functional gains tend to be achieved during the first 12 weeks. Cognitive function tends to improve earlier than motor function, with the most substantial gains occurring within the first 3 weeks. From 12 to 24 weeks there are observable numerical gains in patient functionality, highlighting the need to maintain an adequate rehabilitation program.

Clinical Rehabilitation Impact: This study provides insight into the recovery timeframe for stroke patients, which can support the development of more effective rehabilitation programs.

Keywords: Stroke, Rehabilitation, Functionality, Functional Capacity, Upper limb

INTRODUCTION

Stroke is a major cause of short-term functional impairment in developed countries, which can lead to significant long-term functional impairment in the absence of adequate treatment and rehabilitation.[1–4] Up to 70% of stroke patients show hemiparesis in the acute phase and 40% of those do not regain independency in the execution of activities of daily living (ADL) within the first 6 months after stroke.[5–8]

Cognitive and motor impairments are major causes of disability after stroke.[8,9] Cognitive impairment can, by itself, result in long-term patient dependency, but most frequently, patients regain cognitive function shortly after stroke and continue to reveal motor impairment for longer periods.[9–11] Lack of control of the extremities is usually the main driver of motor impairment in this context. While 65% patients show full recovery of lower limb function, recovering upper limb function is generally more difficult. Some studies indicate that only 15% of patients actually recover hand function, which significantly impacts the execution of ADLs and, consequently, overall quality of life.[5,6,8]

Despite the impact of stroke on functional capacity, the timeframes for functional recovery after stroke are not fully established. Most authors agree the vast majority of functional gains tend to occur in the first weeks after the acute episode, but there is no consensus on the timeframe from which substantial gains should no longer be expected.[4–6,8,12,13] Some studies suggest that recovery tends to plateau at 4 weeks after stroke, but others note meaningful recovery at least until 12 weeks.[5,6,8,14] In any case, few studies actually evaluated long-term functional recovery after an acute episode of stroke, which is a significant limitation when designing stroke rehabilitation programs.

Therefore, there is a need to accurately assess the level of functional recovery over longer periods of time. Better establishing the timeframes in which patients are expected to show greater functional gains would help allocate resources more effectively, providing the basis for better follow-up and treatment. This type of evaluation should use standardised scales that could be easily applied in clinical practice to assist in the development of highly effective treatment and rehabilitation programs, with the ultimate goal of ensuring that all patients reach their full recovery potential.

This study aims to evaluate the progression of functional recovery during the first 24 weeks after acute ischaemic stroke, in order to determine the timeframes for (a) motor, (b) cognitive, and (c) overall recovery.

MATERIALS AND METHODS

Study design and sample

We conducted a prospective observational study of patients hospitalised for acute ischaemic stroke in a tertiary care centre in central Portugal (Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal).

All patients with age 18–85 years and clinical and radiological evaluation indicative of ischaemic stroke in the territory of the middle cerebral artery (confirmed through head CT) were eligible to participate. Patients were excluded from the study if symptom onset occurred more than 3 hours prior to hospital admission, if there were signs of haemorrhagic transformation, if the they showed pre-morbid disability (mRS>2), and if there were other neurological, inflammatory, or neoplastic conditions.

After enrolment, patients underwent a standard treatment and rehabilitation program for 24 weeks, according to routine clinical practice. Functionality assessments were conducted at 48h, 3 weeks, 12 weeks, and 24 weeks after acute stroke.

The study was evaluated and approved by the Scientific Council of the Ethics Committee of the Faculty of Medicine of the University of Coimbra (reference letter 104-CE-2014). Patients or their legal representatives provided their written informed consent prior to enrolment in the study.

Treatment and rehabilitation

During the period of the study, patients received treatment according to routine clinical practice and underwent a closely-controlled rehabilitation program. In the first 12 weeks participants received inpatient care at the study centre, which included 60 minutes of physical therapy, 30 minutes of occupational therapy, and 30 minutes of speech therapy (if aphasia was present) daily. Between week 12 and 14 patients were discharged, following clinical assessment, and continued as outpatients until week 24. After discharge, patients were instructed to continue the daily rehabilitation program at home, including 60 minutes of physical therapy, 30 minutes of occupational therapy, and 30 minutes of speech therapy (if aphasia was present). The study team made all reasonable efforts to ensure patients complied with the rehabilitation program.

Neurological rehabilitation exercises included balance-coordination training, hand rehabilitation, stretching and relaxation exercises, walking exercises, and posture exercises.[15] Exercises focused mainly on using an affected limb, symmetric weight bearing and transfer, mat activity, and gait training.[5]

Functional assessment

Clinical and demographic characteristics were assessed after admission, during the initial clinical evaluation, by a neurologist. Then, patient functionality was assessed over time using several scales at 4 different time points: (1) 48 hours, (2) 3 weeks, (3) 12 weeks, and (4) 24 weeks after stroke. These scales included the modified Rankin Scale (mRS), the Functional Independence Measure (FIM), and the Stroke Upper Limb Capacity Scale (SULCS).

mRS is a widely used assessment scale that evaluates the degree of disability and dependency in activities of daily living.[6] The scale is divided into 7 degrees of ascending disability, in which 0 corresponds to patients with no visible symptoms of disability and 6 corresponds to death. In this study, the Portuguese validated version of mRS was used.

FIM allows the measurement of disability in both physical and cognitive dimensions.[16] The scale consists of 18 items scored 1 to 7, in which higher scores indicate higher degree of functioning and independence in executing ADLs. The items fall into 2 domains: (1) motor domain (M-FIM), which evaluates self-care, sphincter control, transfers, and locomotion, and (2) cognitive domain (C-FIM), which evaluates communication and social cognition. The Portuguese translation of FIM currently recommended by the National Health General Directorate was used.

SULCS is a unidimensional, hierarchical scale specifically designed to evaluate upper limb functioning in stroke patients.[17,18] It is based on the execution of 10 tasks of increasing difficulty. The score corresponds to the number of tasks the patient is able to execute. Scores 0–3 indicate no hand function, scores 4–7 indicate basic hand function, and scores 8–10 indicate good hand function. The recently published Portuguese version of SULCS was used in this study.[17]

Statistical analysis

Quantitative variables are presented as mean ± SD if normality of distribution is confirmed through the Shapiro-Wilk test or otherwise presented as median plus 25^{th}, 75^{th} percentiles. Categorical variables are presented as absolute and relative frequencies.

Changes in functionality throughout the study period were assessed with 5 variables: mRS, SULCS, Motor-FIM, Cognitive-FIM, and Total-FIM. To test for changes in these variables over time, one-way repeated measures analysis of variance (ANOVA) or the Friedman test were applied as appropriate.

In a later phase, measured scores were transformed in percentages of the maximum score for each variable, to assess the relative change in functionality observed in different scales. Two-way repeated measures ANOVA was applied, considering the interaction of time with the several functionality variables.

IBM SPSS Statistics version 23 (IBM Corp, Armonk, NY, USA) was used for statistical analysis, adopting a 5% significance level.

RESULTS

Study population

A total of 556 patients were admitted to the study centre during the enrolment period with acute stroke. Of those, 166 patients fulfilled the selection criteria and were enrolled in the study (**Figure 8.1** details the reasons for exclusion of the remaining patients). Later, 35 patients were excluded from the final analysis population (N=131), due to haemorrhagic transformation (n=10), loss to follow-up (n=14), and death (n=11).

Table 8.1 summarises the demographic and clinical characteristics of participants. Mean ± standard deviation age in the study population was 68.82 ± 11.88 years. Genders were overall evenly represented, but women tended to be older than men, being overrepresented in the 66–79 and ≥80 age strata (p=0.002). The most frequent comorbidities were hypertension, dyslipidaemia, and atrial fibrillation. Older patients tended to show higher rates of atrial fibrillation, hypertension, and diabetes, while younger patients tended to show higher rates of dyslipidaemia, hyperuricemia, obesity, and heart failure. However, these trends were mostly non-significant, except of atrial fibrillation (p=0.031).

Functional recovery over 24 weeks post-stroke

Table 8.2 presents median scores observed in all functional assessments applied in the study. Over the study period patient functionality improved significantly ($P < 0.001$) as measured by all scales. From 48 hours to 3 weeks there were significant functional improvements for all assessment scales. From 3 weeks to 12 weeks there were also significant functionality improvements for all scales, except C-FIM. Finally, during the outpatient period, from 12 weeks to 24 weeks, there were no statistically significant functional improvements for any scale, although median scores were numerically higher for all scales at 24 weeks compared to 12 weeks.

Table 8.3 presents the results of repeated measures two-way ANOVA, which revealed a significant interaction ($P < 0.001$) between the different scales used and follow-up time points. These results indicate significantly different rates of recovery for the different facets of patient functionality assessed by these scales.

Table 8.4 provides a comparison of functional gains measured through the various scales, expressed as percentage of the maximum score, and **Figure 8.2** provides a visual representation of the relative gains over 24 weeks post-stroke. Cognitive impairment was less severe than motor disability in the acute phase. C-FIM scores at 48 hours were significantly higher than M-FIM and mRS scores, and

remained higher for the different time points, although the differences tended to be reduced overtime. Laterality did not significantly affect cognitive function at the different time points ($P>0.05$). Patients with aphasia (n=64) showed significantly worse cognitive function compared to those without aphasia at 48 hours ($P<0.001$) and 3 weeks ($P<0.001$); at 12 and 24 weeks differences were non-significant.

At 48 hours, scores for both M-FIM and mRS were very low in comparative terms—not even reaching 20%, compared to 43% for C-FIM—but improved vastly at 3 weeks and continued to show functional gains at 12 weeks and 24 weeks, though in the later phase the rate of improvement was substantially reduced. Upper limb functioning measured by SULCS, showed a somewhat intermediate degree of disability compared to the previously mentioned cognitive and motors facets of patient functionality. Importantly, SULCS percentage scores were significantly higher than mRS scores at 48 hours. The rates of improvement overtime with SULCS score were comparable to those of C-FIM, with greater improvements in the first 3 weeks followed by more residual gains at 12 and, especially, at 24 weeks.

DISCUSSION

We assessed the long-term functional recovery after acute stroke of the middle cerebral artery and found that significant functional improvements up to 3 months (12 weeks), followed by only numerical improvements until 6 months (24 weeks) after stroke. Cognitive function tends to be less impaired by stroke than motor function and shows early recovery, which occurs mostly within the first 3 weeks. Motor function is severely impacted by stroke and although it shows stark recovery within the first 3 weeks, significant motor function improvements continue to be observed up to 12 weeks, when the rate of recovery is substantially reduced.

The rate of functional recovery observed in study did not follow a linear trend. Overall, patients showed statistically significant functional improvements in the first 3 to 12 weeks, followed by non-significant, lower magnitude improvements from 12 to 24 weeks. Previous studies assessing functional recovery in post-stroke period also identified non-linear rates of recovery.[6] Lee et al.[5] found a very high rate of motor function recovery in the first 4 weeks, which was then somewhat reduced until week 12, at which point 91% of the maximum gains had already been achieved. Verheyden et al.[8] highlighted the first 12 weeks as the most important period for upper and lower limb functional recover, with residual gains until 24 weeks. These results are comparable to our findings, although comparisons with such studies are limited and should be taken with caution, due to the use of different assessment scales, different samples (with both ischemic and haemorrhagic stroke), different clinical characteristics, and different artery territory involved. In the first 3 weeks, the rate of functional recovery was substantially higher than in the remaining periods and after 12 weeks there were no statistically significant improvements, which can be explained by increased neuroplasticity in the first 12 weeks after stroke.[19]

Nonetheless, it is important to consider that there were numerical gains throughout the entire study period. Although these did not reach statistical significance in the aggregate analysis, such numerical differences might still have clinically relevant implications in some patients, which could, ultimately, translate into patients' dependency or independency in the execution of ADLs.

The FIM scale was adopted in this study because it is frequently used in clinical practice and is designed to measure disability in both the cognitive and motor domains.[15,16] In terms of the cognitive domain, it is estimated that 30–50% of patients show cognitive impairment after stroke.[9] Mellon et al.[9] characterised cognitive disability after stroke using Montreal Cognitive Assessment (MoCA) and found that cognitive impairments tend to resolve rapidly after acute stroke. In this study, there were no significant improvements in cognitive function after 3 weeks and approximately 50% of patients continued to show some degree of cognitive impairment 24 weeks after stroke. These results are comparable to our findings. Aydin et al.[15] found that contrary to the cognitive domain, the Total FIM scores (which encapsulate the results of the motor domain) improve significantly until 12 weeks after stroke, which is also comparable to our findings.

The mRS was used because it is one of the most well-established scales in the assessment of patient functionality after stroke.[20] We also adopted SULCS to specifically assess upper limb functionality, since it is one of the most impactful facets of overall functionality for the execution of ADLs.[21] Interestingly, the relative comparison of percentage scores for SULCS and mRS indicates that these scales are not very well correlated. mRS shows significantly lower score overall (in percentage terms), which could be attributed to the inherent characteristics of the scales. However, the rates of improvements in SULCS and mRS appear to be substantially different. At 48 hours SULCS percentage scores were significantly higher, leading to lower rates of improvement compared to mRS until 12 weeks. Such findings indicate that mRS might not accurately encapsulate upper limb functioning in the initial weeks after acute stroke. The types of assessments used in mRS are more geared towards evaluating walking ability and, therefore, upper limb functioning is not as accurately measured as with a specific scale. These findings highlight the importance of using a specific upper limb function assessment scale. Importantly, similarly to the results seen with T-FIM, both SULCS and mRS showed significant gains until 12 weeks after stroke and non-significant numerical gains until 24 weeks, which is in agreement with previous studies.[5,8]

This study has some limitations to consider. The study population is relatively heterogeneous—especially in terms of age—potentially leading to different patterns of functional recovery, although we enrolled a substantially larger sample size than comparable previous studies. The type of rehabilitation received during the study period (12 weeks inpatient daily rehabilitation followed by 12 weeks outpatient daily rehabilitation) can also introduce some limitations when interpreting the functional gains (or lack thereof in the outpatient setting) in the different periods. The observational, routine

clinical practice nature of this study prevented the use of the same type of rehabilitation for the entire duration of the study. Still, this approach follows current best practices for rehabilitation of stroke patients, providing insight into the expected recovery in routine clinical practice. In the future, real-world studies with larger populations and longer follow-up times will be of great interest to establish the patterns of functional recovery and identify the most effective rehabilitation strategies.

CONCLUSIONS

Functional recovery occurs at least until 24 weeks after acute stroke, but most the of the functional gains tend to be achieved during the first 12 weeks, reflecting the well-established period of increased neuroplasticity. Cognitive function tends to improve earlier than motor function, with the most substantial gains occurring within the first 3 weeks. From 12 to 24 weeks there are observable numerical gains in patient functionality, highlighting the need to maintain an adequate rehabilitation program, even if in an outpatient setting.

The patterns of functional recovery after stroke observed here can provide valuable insight to support the development and optimisation of rehabilitation programs, allowing better resource allocation that could improve patient outcomes. Future studies should evaluate functional recovery over longer periods of time in real-word conditions, in order to further establish the threshold over which patients stop experiencing functional gains and the extent to which those gains are maintained overtime

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

FUNDING SOURCE

There were no external sources of funding.

ACKNOWLEDGEMENTS

The authors thank Graça Fernandes, BSN (Stroke Unit, Centro Hospitalar Universitário de Coimbra) for providing nursing care throughout the study; Marisa Loureiro, MSc (Laboratory of Biostatistics and Medical Informatics, Faculty of Medicine of the University of Coimbra) for providing assistance during statistical analysis; and Tiago Campos, MSc (ARC Publishing) for providing editorial assistance.

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TABLES

Table 8.1 – Clinical and demographic characteristics of participants stratified by age.

	Age, yrs			
	18–65 (n=45)	**66–79 (n=63)**	**≥80 (n=23)**	**p-value**
Gender, n (%)				
Female (n=66)	15 (33.3)	33 (52.4)	18 (78.3)	0.002
Male (n=65)	30 (66.7)	30 (47.6)	5 (21.7)	
Comorbidities/lifestyle factors, n (%)				
Atrial fibrillation (n=59)	19 (42.2)	24 (38.1)	16 (69.6)	0.031
Dyslipidaemia (n=59)	22 (48.9)	29 (46.0)	8 (34.8)	0.529
Hypertension (n=91)	26 (57.8)	46 (73.0)	19 (82.6)	0.076
Diabetes (n=38)	10 (22.2)	18 (28.6)	10 (43.5)	0.187
Hyperuricemia (n=16)	6 (13.3)	7 (11.1)	3 (13.0)	0.933
Obesity (n=25)	11 (24.4)	13 (20.6)	1 (4.3)	0.124
Heart failure (n=27)	10 (22.2)	13 (20.6)	4 (17.4)	0.897
Smoking (n=16)	6 (13.3)	8 (12.7)	2 (8.7)	0.847
Laterality, n (%)				
Right (n= 65)	21 (46.7)	32 (50.8)	12 (52.2)	0.882
Left (n= 66)	24 (53.3)	31 (49.2)	11 (47.8)	
Aphasia, n (%)				
Yes (n= 64)	23 (51.1)	27 (42.9)	14 (60.9)	0.312
No (n= 67)	22 (48.9)	36 (57.1)	9 (39.1)	

Table 8.2 – Median scores in patient functionality assessments over the first 24 weeks after stroke.

Assessment scales	Effect of time *P*-value	48 hours	3 weeks	*P*-value (48 h vs. 3 weeks)	12 weeks	*P*-value (3 vs. 12 weeks)	24 weeks	*P*-value (12 vs. 24 weeks)
SULCS (0 – 10)	< 0.001	1 (0; 7)	3 (1; 9)	< 0.001	5 (1; 10)	0.019	6 (3; 10)	NS
mRS (0 – 5)	< 0.001	4 (4; 5)	4 (2; 4)	< 0.001	3 (1; 4)	0.008	2 (1; 4)	NS
M-FIM (13 – 91)	< 0.001	20 (13; 33)	44 (20; 87)	< 0.001	66 (31; 91)	0.002	72 (35; 91)	NS
C-FIM (5 – 35)	< 0.001	16 (5; 30)	23 (13; 31)	0.002	25 (17; 33)	NS	27 (17; 35)	NS
T-FIM (18 – 126)	< 0.001	36 (18; 61)	68 (35; 115)	< 0.001	93 (53; 120)	0.001	96 (56; 123)	NS

C-FIM = Cognitive Functional Independence Measure; M-FIM = Motor Functional Independence Measure, mRS = modified Rankin Scale; SULCS = Stroke Upper Limb Capacity Scale; NS = Non-significant; T-FIM = Total Functional Independence Measure

Table 8.3 – Results of two-way repeated measures analysis of variance.

Variables	Degrees of freedom	F	*P*
Assessment scales	2.332	56.061	< 0.001
Time	2.196	132.940	< 0.001
Assessment scales x time	5.548	22.161	< 0.001

Table 8.4 – Relative change in patient functionality according to different assessment scales.

Assessments scales	48 h		3 weeks		12 weeks		24 weeks	
	Estimate (SE)	95% CI	Estimate (SE)	95% CI	Estimate (SE)	95% CI	Estimate (SE)	95% CI
SULCS	32.75 (3.19)[b,c]	26.45 – 39.05	47.56 (3.39)	40.86 – 54.26	53.66 (3.36)	47.03 – 60.30	59.01 (3.26)	52.56 – 65.45
mRS	16.49 (1.77)[a,d]	12.99 – 19.99	39.85 (3.15)[d]	33.63 – 46.07	48.55 (3.08)[d,e]	42.46 – 54.64	53.74 (3.07)[d]	47.68 – 59.81
M-FIM	17.53 (2.17)[a,d]	13.25 – 21.81	49.34 (3.42)	42.58 – 56.11	60.03 (3.20)	53.69 – 66.37	64.24 (3.31)	57.70 – 70.78
C-FIM	43.05 (3.48)[b,c,e]	36.16 – 49.95	55.52 (3.06)[b]	49.47 – 61.58	63.46 (2.79)[b]	57.93 – 68.99	66.77 (2.71)[b]	61.41 – 72.12
T-FIM	24.63 (2.37)[d]	19.94 – 29.31	50.80 (3.26)	44.35 – 57.24	61.30 (2.99)[b]	55.38 – 67.22	64.90 (3.01)	58.95 – 70.85

Data presented as percentage of the maximum score for each scale, summarised here as mean (standard error) and 95% Confidence interval.
C-FIM = Cognitive Functional Independence Measure; CI = Confidence Interval; M-FIM = Motor Functional Independence Measure, mRS = modified Rankin Scale; SE = Standard error; SULCS = Stroke Upper Limb Capacity Scale; T-FIM = Total Functional Independence Measure
Post-hoc multiple comparison analysis:
[a]Significant versus SULCS;
[b]Significant versus mRS;
[c]Significant versus M-FIM;
[d]Significant versus C-FIM;
[e]Significant versus T-FIM.

FIGURES

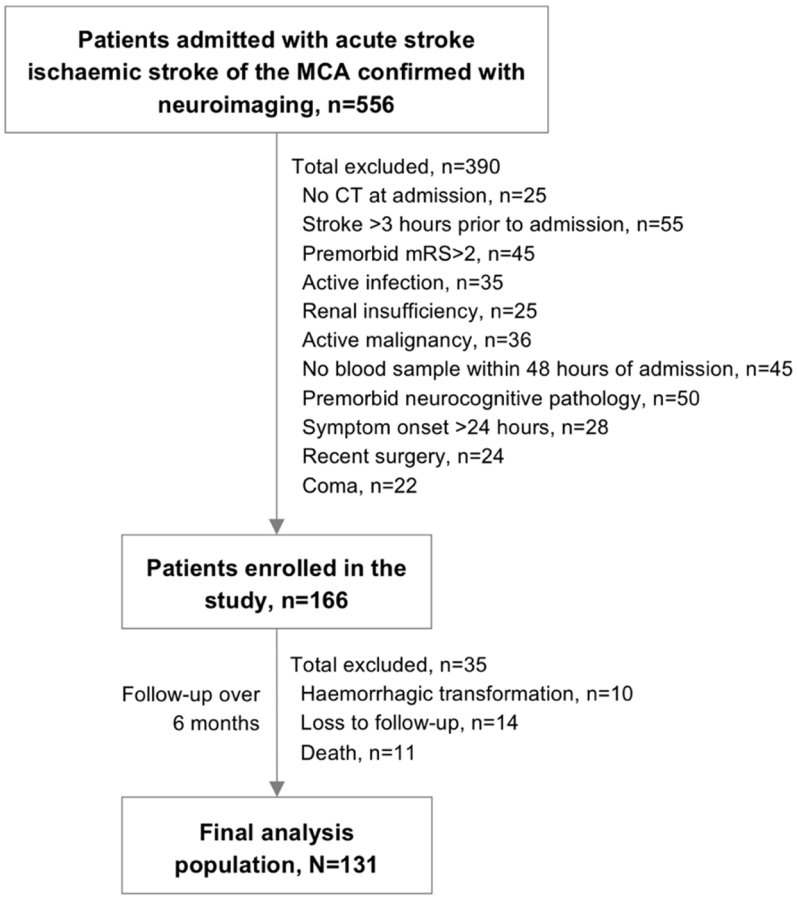

Figure 8.1 – Study flowchart.

MCA = Middle cerebral artery

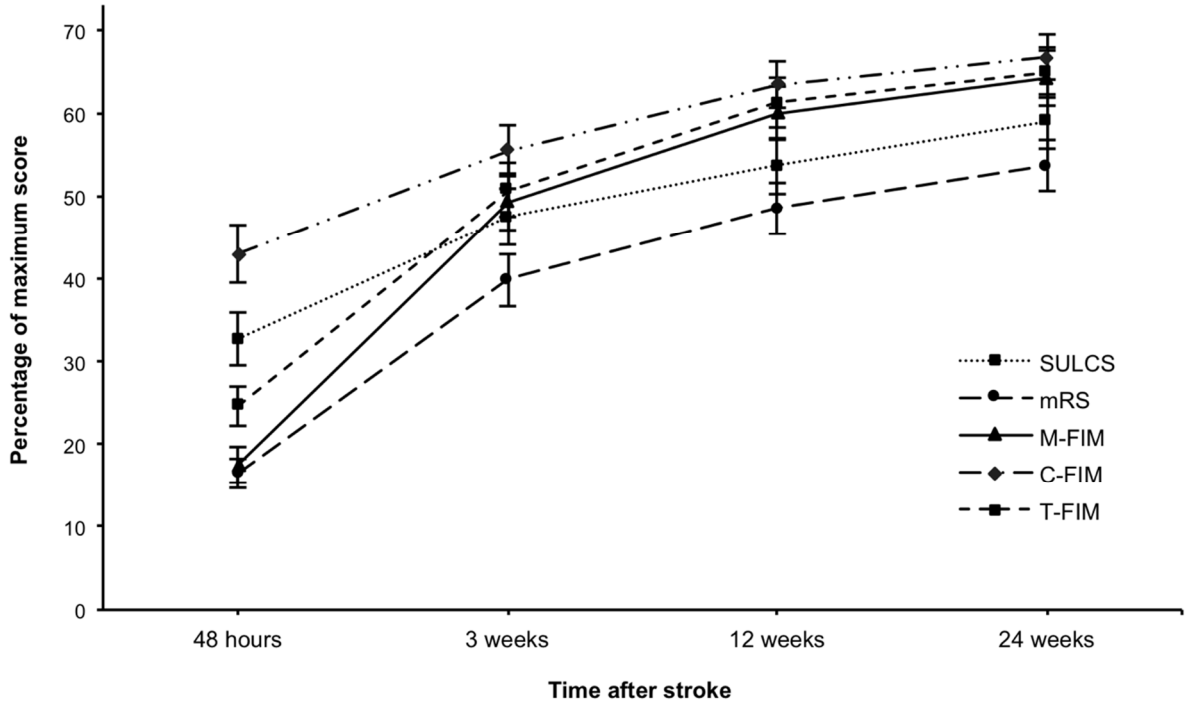

Figure 8.2 – Comparison of the percentage of functional gains according to different assessment scales.

See table 8.4 for post-hoc analysis results.
C-FIM = Cognitive Functional Independence Measure; M-FIM = Motor Functional Independence Measure, mRS = modified Rankin Scale; SULCS = Stroke Upper Limb Capacity Scale; T-FIM = Total Functional Independence Measure

CHAPTER 9

IMPACT OF POST-STROKE RECANALIZATION ON GENERAL AND UPPER LIMB FUNCTIONING

Submitted as:

Impact of post-stroke recanalization on general and upper limb functioning: a prospective, observational study

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Submitted: Annals of Rehabilitation Medicine

Impact of post-stroke recanalization on general and upper limb functioning: a prospective, observational study

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ABSTRACT

Objective: To assess the impact of recanalization (spontaneous and therapeutic) on upper limb functioning and general patient functioning after stroke.

Methods: This is a prospective, observational study of patients hospitalized due to acute ischemic stroke in the territory of the middle cerebral artery (n=98). Patients completed a comprehensive rehabilitation program and were followed-up for 24 weeks. The impact of recanalization on patient functioning was evaluated using the modified Rankin Scale (mRS) and Stroke Upper Limb Capacity Scale (SULCS).

Results: General and upper limb functioning improved markedly in the first 3 weeks after stroke. Age, gender, and National Institutes of Health Stroke Scale (NIHSS) score at admission were associated with general and upper limb functioning at 12 weeks. Successful recanalization was associated with better functioning. Among patients who underwent therapeutic recanalization, NIHSS scores ≥16.5 indicate lower general functioning at 12 weeks (sensibility=72.4%; specificity=78.6%) and NIHSS scores ≥13.5 indicate no hand functioning at 12 weeks (sensibility=83.8.4%; specificity=76.5%).

Conclusions: Recanalization, either spontaneous or therapeutic, has a positive impact on patient functioning after acute ischemic stroke. Functional recovery occurs mostly within the first 12 weeks after stroke, with greater functional gains among patient with successful recanalization. Higher NIHSS scores at admission worse functional recovery.

Keywords: Stroke; Recanalization; Rehabilitation; Functioning; Upper limb; Functionality

INTRODUCTION

Stroke is a leading cause of functional disability in the western world. Most patients surviving an acute stroke present hemiparesis of brachial predominance, which constitutes a major challenge in the rehabilitation program and often leads to long-term disability (1).

Most acute strokes are of ischaemic aetiology (2,3) and among those, patients with the cardioembolic subtype (approximately 25%) tend to show worse clinical and functional prognosis, with higher in-hospital mortality in the acute phase and worse functioning at discharge (4,5). Revascularisation of at-risk brain tissue (ischaemic penumbra area) is considered an important predictor of both clinical and functional recovery post-stroke (6). Cell viability is maintained for a few hours after acute stroke and function can be recovered if blood flow is restored in an adequate timeframe (7,8). The restoration of vessel patency (vascular permeability) at the site of occlusion, termed recanalization, can occur spontaneously or as a result of a therapeutic intervention. Spontaneous recanalization occurs in up to 67% of ischaemic strokes, mostly within the first 48 hours (9). The factors determining spontaneous recanalization are still poorly understood, but atrial fibrillation is associated with lower rate of spontaneous recanalization, while stage 3 hypertension is associated with higher rates of spontaneous recanalization (9).

Several therapeutic recanalization techniques—broadly classified as chemical or mechanical—have been developed to ensure reperfusion of injured brain tissue as quickly and effectively as possible (9,10). However, different factors may limit the effectiveness of revascularization techniques. Early access to revascularization treatment is associated with better long-term functional outcome (11), while factors such as age, severe neurological impairment, and delayed endovascular treatment are associated with worse functional prognosis even if recanalization is achieved (12).

Studies in this field have evaluated functional outcomes based on general functioning assessment tools such as the modified Rankin Scale (mRS) (11,13,14) and found recanalisation to be strongly associated with improved general functional outcome (15). These tools characterise general patient functioning but are not well-suited to assess specific domains of patients' functioning, such as upper limb functioning. From a rehabilitation standpoint, upper limb function is critically important, since it will establish the ability of patients to regain autonomy. Therefore, it is important to specifically establish the impact of recanalization on upper limb function in addition to the global patient functioning.

This study aims to assess the impact of recanalization (spontaneous and therapeutic) on upper limb functioning and general patient functioning after ischaemic stroke of the middle cerebral artery.

METHODS

Study design and selection criteria

This was a prospective, observational study of patients hospitalised due to acute ischaemic stroke in a national rehabilitation centre in the central region of Portugal. Patients could be included in the study if they were 18–85 years old and had acute ischaemic stroke in the territory of the middle cerebral artery (confirmed through head computed tomography [CT]). Patients were excluded from participating in the study if they did not reach the emergency department (ED) within the first 3 hours after symptom onset, if they had signs of haemorrhagic transformation, if they had pre-morbid mRS >2, if they showed other neurological, inflammatory, or neoplastic comorbidities, and if they did not completed head CT at admission.

After enrolment in the study, patients underwent routine clinical practice procedures for neurological and physical rehabilitation (including recanalization procedures as appropriate). Patients completed a comprehensive rehabilitation program lead by physiatrist, based on current international guidelines for the rehabilitation of stroke patients, according to the clinical practice of the study centre. The program started at the second day after admission and included treatments at the nursing sector of rehabilitation, physiotherapy, and occupational therapy. Patients were followed-up for up to 24 weeks.

The study received favourable opinion by the Scientific Council of the Ethics Committee of the Faculty of Medicine of the University of Coimbra, Coimbra, Portugal (reference letter 104-CE-2014). All patients or their legal representatives provided their written informed consent prior to inclusion in the study.

Recanalization criteria and procedures

On admission to the ED, patients underwent standard imaging studies including head CT and head Magnetic Resonance Imaging (MRI) when needed. The recanalization therapies used were intravenous thrombolysis alone, thrombectomy alone or the combination of the two, following the guidelines of the European Stroke Organization (16–18).

In patients who underwent fibrinolysis, the evaluation of recanalization was done through Transcranial Doppler (TD) and recanalization was assumed for grades 4 and 5 of the Thrombolysis in Brain Ischemia (TIBI) grading scale (19). TD was done by the same physician for all patients.

Spontaneous recanalization was established using the same criteria among patients who did not underwent therapeutic recanalization procedures.

Clinical and functional assessment

Patients were invited to participate in the study after admission to the ED and were followed up for 24 weeks, while receiving a treatment and rehabilitation program according to routine clinical practice.

Demographic and clinical data were collected for each patient upon inclusion in the study, including age, gender, stroke subtype according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification (20), severity of stroke according to National Institutes of Health Stroke Scale (NIHSS) (21), and presence of atrial fibrillation or hypertension.

Functional assessment was done using two clinically validated scales: a general functioning assessment scale, mRS, and a specific upper limb functioning assessment scale, Stroke Upper Limb Capacity Scale (SULCS) (22,23). Evaluations of patient functioning (with mRS and SULCS) were completed at 4 different times: (1) 48 hours, (2) 3 weeks, (3) 12 weeks, and (4) 24 weeks post-stroke. For the purposes of analysis, mRS results were dichotomized into "Low functioning" (score 3–5) and "Good functioning" (scores 0–2). SULCS scores were dichotomized into “No hand functioning” (scores 0–7) and “Good hand functioning” (scores 8–10). In this context, we opted for a dichotomization that allowed proper differentiation of distal function (i.e. if the patient had advanced hand function), since distal function is highly impactful in terms of overall functional capacity and quality of life (23).

Rehabilitation interventions

During the period of the study, patients received treatment according to routine clinical practice and underwent a closely controlled rehabilitation program, following current clinical practice in the study center. During the 12 weeks participants received inpatient care at the study center, which included 60 minutes of physical therapy, 30 minutes of occupational therapy, and 30 minutes of speech therapy (if aphasia was present) daily, 5 days per week. Patients who achieved maximum scores for all assessment scales and did not need further medical care, were discharged and then reevaluated at 12 weeks.

Neurological rehabilitation exercises included balance-coordination training, hand rehabilitation, stretching and relaxation exercises, walking exercises, and posture exercises. Exercises focused mainly on using the affected limb, symmetric weight bearing and transfer, mat activities, and gait training.

Statistical analysis

Qualitative variables were summarised by their absolute and relative frequencies, while quantitative variables were summarised by the median, 1st and 3rd quartiles, minimum, and maximum. Mann-Whitney and Chi-square tests were used for bivariate analysis, and Monte Carlo simulations were performed where appropriate. ROC analysis was used to evaluate the discriminative power of NIHSS scores for general patient functioning and upper limb functioning.

All analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp, Armonk, NY, USA). A 5% significance level was used.

RESULTS

Characteristics of the study population

During the period of the study, 115 patients were admitted with acute ischaemic stroke fulfilling the selection criteria, and provided their informed consent to participate in the study. After inclusion, however, 17 patients were withdrawn from the study due to haemorrhagic transformation (n=5), death (n=7), and loss to follow-up (n=5), thus leading to a final study population of 98 patients with 24 weeks of follow-up.

Table 9.1 presents the demographic and clinical characteristics of the sample. Median age was 70 years, with a slight female predominance (54.1%). Half the sample had atrial fibrillation, while hypertension was more frequent (65.3%). Most patients had stroke of cardioembolic subtype (53.1%). Most patients had occlusion in a distal MCA segment (54.1%) and right lateralisation (54.1%). The median score in NIHSS at admission was 14 (Q1: 7; Q3: 20). Overall, 69.4% of patients underwent a recanalization technique—intravenous fibrinolysis and/or endovascular thrombectomy—within a few hours after the lesion.

General functioning (measured through mRS) improved markedly in the first 3 weeks after stroke: from 15.3% of patients with good functioning at 48 hours to 43.9% at 3 weeks. Then, general functioning plateaued at 12 weeks with 55.1% of patients showing good functioning. Upper limb functioning (measured through SULCS) showed a similar evolution over time, however the range of improvement was substantially smaller. At 48 hours 17.6% of patients showed good hand functioning, improving to 38.8% at 3 weeks, but plateauing at approximately 44%.

Table 9.2 presents the level of general functioning and upper limb functioning at 12 weeks according to patients' characteristics. Age, gender, and NIHSS at admission were significantly associated with general and upper limb functioning at 12 weeks. The segment of occlusion was also significantly associated, specifically, with upper limb functioning at 12 weeks, while for general functioning the association did not reach statistical significance. Atrial fibrillation, hypertension, stroke subtype (cardioembolic vs. all others), and, importantly, the use of a recanalization technique were not significantly associated with functioning at 12 weeks.

Recanalization and functioning

Recanalization was achieved in 57.1% of patients: 11.2% of patients showed spontaneous recanalization, while 45.9% of patients showed successful therapeutic recanalization (corresponding a rate of successful therapeutic recanalization of 63.4%). **Table 9.3** explores the success of recanalization (spontaneous or therapeutic) according to the clinical characteristics of patients. The use of a

recanalization technique and NIHSS score at admission were significantly associated with the success of recanalization.

Table 9.4 presents the evolution of patient functioning according the presence of successful recanalization and the type of recanalization (spontaneous vs. therapeutic). The proportion of patients with good general functioning was significantly higher among those with successful recanalization: 64.3% of patients with successful recanalization showed good general functioning at 24 weeks, compared to 42.9% of those without recanalization (*P*=0.035). A similar trend was observed for upper limb functioning: 55.4% of patients with successful recanalization showed good hand functioning at 24 weeks, compared to 28.6% of those without recanalization (*P*=0.008). Patients who achieved recanalization after a therapeutic intervention showed significantly better general functioning than those who had spontaneous recanalization at 3, 12, and 24 weeks. In terms of upper limb functioning, patients who achieved successful therapeutic recanalization also showed significant better functioning at 12 and 24 weeks, compared to those who had spontaneous recanalization.

Table 9.5 explores the levels of general and upper limb functioning at 12 weeks in patients with successful recanalization according to their demographic and clinical characteristics. Similarly to the overall population, among those with successful recanalization, the factors associated with good general and upper limb functioning at 12 weeks were age, gender, and NIHSS at admission. Here, however, the use of a recanalization technique was also significantly associated with better general (*P*=0.032) and upper limb functioning (*P*=0.041), which was not observed for the overall population.

To establish the discriminative power NIHSS scores at admission for patient functioning after stroke (12 weeks) in those patients in which a recanalization technique had been applied, ROC analysis was employed. For general functioning, NIHSS scores ≥16.5 indicate lower general functioning at 12 weeks (sensibility=72.4%; specificity=78.6%; AUC=0.761 [CI 95%: 0.643–0.880], *P*<0.001), despite the use of a therapeutic recanalization technique. For upper limb functioning, NIHSS scores ≥13.5 indicate no hand functioning at 12 weeks (sensibility=83.8.4%; specificity=76.5%; AUC=0.812 [CI 95%: 0.706–0.918], *P*<0.001), also despite the use of a therapeutic recanalization technique. **Figure 9.1** presents ROC curves for both analyses.

DISCUSSION

In this study, we assessed the impact of recanalization—both spontaneous and therapeutic—on patient functioning up to 6 months after acute ischemic stroke. Occurrence of successful recanalization was significantly associated with better general functioning as well as upper limb function from 48 hours to 6 months after stroke. The use of therapeutic recanalization techniques was only associated with better general and upper limb functioning when recanalization was actually achieved. This is to our knowledge one of the few studies validating the specific impact of successful recanalization on

upper limb function, which is of critical importance in the recovery of patient autonomy in the long-term.

The success of therapeutic recanalization has been associated with good functional prognosis in previous studies, and is one of the main predictors of good functioning at 12 weeks after stroke (11,13,14,17,24). Intravenous thrombolysis with rt-PA achieves successful recanalization in 13% to 50% of large vessel occlusions (25), while endovascular thrombectomy achieves successful recanalization in up to 54% of cases, which is most evident in occlusions of large vessels (26–28). Some studies also showed the superiority of combined treatment: mechanical thrombectomy in combination with recombinant tissue plasminogen activator (rt-PA) in large vessel occlusions (25,29). In this study, most patients that underwent fibrinolysis and/or thrombectomy achieved successful recanalization (63.4%), a slightly higher rate than expected according to the literature. On the other hand, most patients (53.3%) that did not underwent a therapeutic recanalization technique did not show successful recanalization, as expected.

Several demographic and clinical characteristics were associated with recanalization success and patient functioning in this study. Advanced age is frequently associated with worse clinical and functional prognosis after stroke, due to frequent comorbidities and lower rehabilitation potential (30). In this study, while increasing age was, in fact, associated with worse patient functioning, there was no discernible impact on recanalization success. A similar trend was seen for the female gender, with worse general and hand functioning at 12 weeks and no significant difference on recanalization success. This is consistent with previous studies (31,32). Several factors have been suggested as potential causes of worse functioning in women, such as more serious neurological impairment presentation and lower likelihood of receiving acute stroke treatment. However, previous analysis of current evidence failed to identify the causal factors (32). Additionally, Boheme et al. concluded that after adjustment for age, NIHSS at admission, and tPA use, the gender difference was no longer statistically significant (31). In this study, we implemented an early and intensive rehabilitation program aimed at allowing patients to reach their full recovery potential. The use of early and high-intensity standardized rehabilitation programs have been found to significantly improve functional outcome after stroke (33). Innovative rehabilitation interventions are currently under study—including technology-based interventions—with promising early results (34). Such interventions could prove to be valuable tools both to address direct patient needs as well as to tackle resource constrains in healthcare systems.

The rate of successful recanalization after administration of rt-PA is expected to be lower in patients with atrial fibrillation (30). A recent study indicates that patients with atrial fibrillation are less likely to benefit from rt-PA, but atrial fibrillation might also lead to greater effectiveness of mechanical thrombectomy (30). In this sample, however, we did not found atrial fibrillation to significantly impact

either the rate of recanalization or the level of patient functioning. This lack of association could be because thrombus in patients with atrial fibrillation, while larger in size, tend to be easier to remove.

Previous studies indicate that patients with stroke of cardioembolic origin are less likely to have successful recanalization, which leads to worse overall prognosis (35,36). In this study, however, we were not able to identify a significant impact of the cardioembolic subtype of stroke on either recanalization success or patient functioning. The lack of significant impact could conceivably be related to the dichotomization adopted (cardioembolic vs. non-cardioembolic), which does not account for variability between patients in the "non-cardioembolic" category.

Hypertension was found to influence both the occurrence of recanalization as well as the functional outcome (9,37). In this study, however, we were not able to identify such relationships. This could be explained by the non-linear relationships identified in previous studies (9,37), which would require larger sample sizes to identify these effects.

Occurrence of successful recanalization significantly impacted general patient functioning over the study period, which is in accordance with previous findings. Chaudhuri et al. studied functional outcome after intra-arterial fibrinolysis and found a significant improvement in general functioning at 12 weeks (14). Bhatia et al. demonstrated that recanalization success was significantly associated to functional outcome, adding that earlier recanalization lead to significantly improved functional outcomes (11). Gadow et al. conducted a retrospective study that included patients who underwent both recanalization techniques and demonstrated that all patients with good functioning (mRS score ≤ 2) at 12 weeks had successful recanalization (13), the criteria for recanalization were similar to those used in the present study (TICI$\geq$2b).

Successful recanalization also specifically impacted upper limb functioning as measured through SULCS. We were not able to find other studies specifically evaluating the impact of recanalization on upper limb functioning, but this is a critically important facet of patient function that can have great implications for patient autonomy and overall quality of life. This study demonstrates that successful recanalization is crucial to improve upper limb function after stroke.

This study has several limitations. It was conducted in a highly specialised stroke unit and, therefore, this population might not be representative of other clinical care settings. While the selection criteria were considerably broad, patients with $\geq$85 years were excluded in an effort to avoid the bias posed by significant comorbidity and co-medication profiles, but it would be important to study this population in future studies. The sample size also introduces some limitations, especially for patients with spontaneous recanalization. The use of ultrasound to access recanalisation can potentially introduce limitations in terms of accuracy and other neuroimaging modalities (such as angio-CT or angio-MRI) could provide additional data. However, these modalities would involve the need to expose the patients to more contrast agents and radiation and we wanted to avoid overexposure. The use of CT

imaging is also a potential limitation to consider; this type of imaging was, nonetheless, used since it would be more representative of routine clinical practice. Additionally, there are other parameters including time metrics that could have an impact on functional outcomes given the importance of early therapeutic intervention for recanalisation. These parameters were, however, not prospectively collected in this study, but should be considered in further analysis of the impact if recanalisation on upper limb functioning. Finally, the instruments used to assess functionality have limitations associated with their biometric characteristics.

In conclusion, recanalization, either spontaneous or therapeutic, has a positive impact on patient functioning after acute ischemic stroke. Functional recovery occurs mostly within the first 12 weeks after stroke, with greater functional gains among patient with successful recanalization, both in terms of general functioning and, specifically, upper limb functioning. For patients who underwent a recanalization procedure, a NIHSS score at admission ≥17 predicts low general functioning at 12 weeks (mRS 3–5) and NIHSS scores at admission ≥14 predict no hand functioning at 12 weeks (SULCS 0–7), despite the use of a recanalization technique.

Further studies should be conducted to validate these findings in larger study populations, preferably in multicenter settings. Such studies should assess the specific impact of acute care procedures on long term general and upper limb functioning to improve treatment and rehabilitation strategies that allow stroke patients to restore their functioning to the highest degree possible.

ETHICAL APPROVAL

The study received favourable opinion by the Scientific Council of the Ethics Committee of the Faculty of Medicine of the University of Coimbra, Coimbra, Portugal (reference letter 104-CE-2014). All patients or their legal representatives provided their written informed consent prior to inclusion in the study.

CONFLICTS OF INTEREST

The authors have no conflict of interest to declare.

FUNDING

There were no external sources of funding.

ACKNOWLEDGEMENTS

The authors thank Graça Fernandes, BSN (Stroke Unit, Centro Hospitalar Universitário de Coimbra) for providing nursing care throughout the study; Marisa Loureiro, MSc (Laboratory of Biostatistics and Medical Informatics, Faculty of Medicine of the University of Coimbra) for providing assistance during statistical analysis; and Tiago Campos, MSc (PMA – Pharmaceutical Medicine Academy) for providing editorial assistance.

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FIGURES

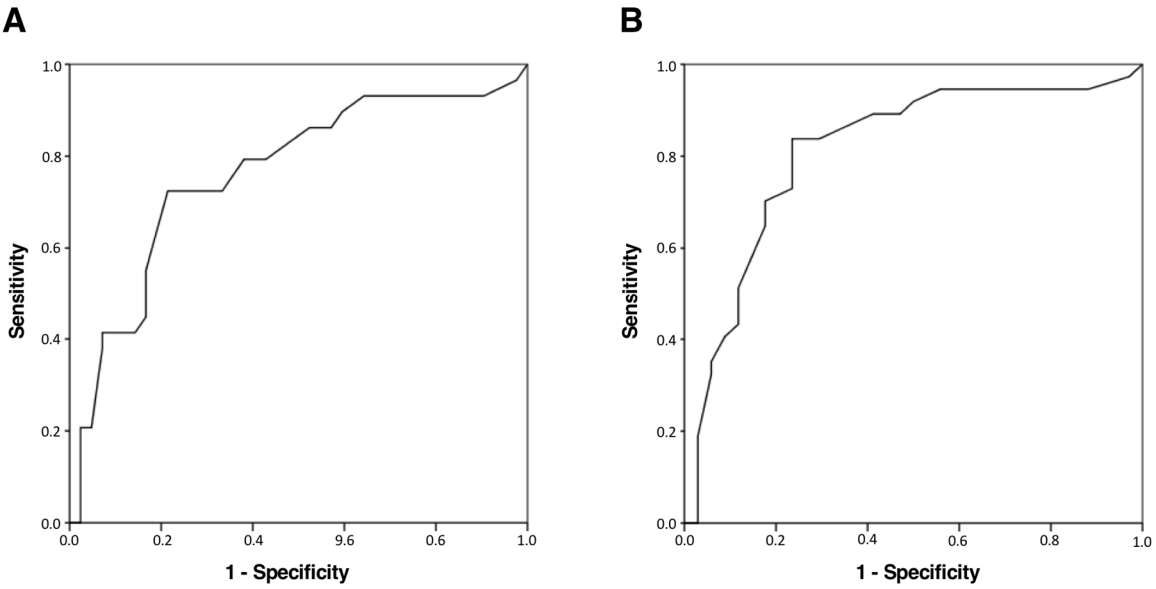

Figure 9.1 – ROC curves for (A) low general functioning (mRS) and (B) no hand functioning (SULCS) at 12 weeks according to NIHSS scores at admission.

mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale (NIHSS); ROC = Receiver operating characteristic; SULCS = Stroke Upper Limb Capacity Scale

TABLES

Table 9.1 – Clinical and demographic characteristics.

Characteristics	Study population (n=98)
Age	
Median (Q1; Q3)	70.0 (62.3; 78.0)
NIHSS at admission	
Median (Q1; Q3)	14.0 (7.0; 20.0)
Gender, n (%)	
Male	45 (45.9)
Female	53 (54.1)
Atrial fibrillation, n (%)	
Yes	49 (50.0)
No	49 (50.0)
Hypertension, n (%)	
Yes	64 (65.3)
No	34 (34.7)
Fibrinolysis n (%)	
Yes	68 (69.4)
No	30 (30.6)
Stroke subtype (TOAST), n (%)	
Cardioembolic	52 (53.1)
Non-cardioembolic	46 (46.9)
Segment, n (%)	
Proximal (M1)	45 (45.9)
Distal (M2, M3)	53 (54.1)
Laterisation, n (%)	
Right	53 (54.1)
Left	45 (45.9)
Therapeutic recanalization technique, n (%)	
Yes	71 (72.4)
No	27 (27.6)
Successful therapeutic recanalization, n (%)	
Yes	45 (63.4)
No	26 (36.6)
Type of recanalization, n (%)	
Spontaneous	11 (11.2)
Therapeutic	45 (45.9)
Good general functioning (mRS 0–2), n (%)	
48 hours	15 (15.3)
3 weeks	43 (43.9)
12 weeks	54 (55.1)
24 weeks	54 (55.1)
Good hand functioning (SULCS 8–10), n(%)	
48 hours	27 (27.6)
3 weeks	38 (38.8)
12 weeks	44 (44.9)
24 weeks	43 (43.9)

mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale (NIHSS); SULCS = Stroke Upper Limb Capacity Scale; TOAST = Trial of ORG 10172 in Acute Stroke Treatment (TOAST

Table 9.2 – Patient functioning 12 weeks after stroke for the overall population, according to patients' clinical characteristics.

Characteristics	Good General Functioning (mRS 0 – 2)			Good Hand Functioning (SULCS 8 – 10)		
	Yes (n=54)	No (n=44)	*P-value*	Yes (n=44)	No (n=54)	*P-value*
Age, median (Q1; Q3)	67.0 (58.5; 74.5)	74.0 (64.0; 81.0)	<0.001	67.0 (58.0; 74.0)	76.5 (66.5; 81.5)	0.003
NIHSS, median (Q1; Q3)	7.5 (6.0; 12.5)	17.0 (14.0; 23.0)	<0.001	11.0 (6.0; 16.0)	17.0 (13.0; 23.0)	<0.001
Female gender, n (%)	21 (38.9)	32 (72.7)	0.001	15 (34.1)	38 (70.4)	<0.001
Atrial fibrillation, n (%)	26 (48.1)	23 (52.3)	0.685	19 (43.2)	30 (55.6)	0.223
Hypertension, n (%)	33 (61.1)	31 (70.5)	0.334	27 (61.4)	37 (68.5)	0.459
Cardioembolic stroke, n (%)	25 (46.3)	27 (61.4)	0.137	19 (43.2)	33 (61.1)	0.077
Therapeutic recanalization technique, n (%)	42 (77.8)	29 (65.9)	0.191	34 (77.3)	37 (68.5)	0.335
Segment (proximal), n (%)	20 (37.0)	25 (56.8)	0.051	13 (29.5)	32 (59.3)	0.003

mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale (NIHSS); SULCS = Stroke Upper Limb Capacity Scale

Table 9.3 – Recanalization success, according to the patients' clinical characteristics.

Characteristics	Recanalization		
	Yes (n=56)	No (n=42)	*P-value*
Age, median (Q1; Q3)	70.0 (64.0; 78.5)	69.5 (59.0; 77.0)	0.659
NIHSS, median (Q1; Q3)	12.5 (6.50; 17.50)	17.0 (12.0; 23.0)	0.019
Female gender, n (%)	28 (50.0)	25 (59.5)	0.349
Atrial fibrillation, n (%)	27 (48.2)	22 (52.4)	0.683
Hypertension, n (%)	35 (62.5)	29 (69.0)	0.500
Cardioembolic stroke, n (%)	28 (50.0)	24 (57.1)	0.483
Therapeutic recanalization technique, n (%)	45 (80.4)	26 (61.9)	0.043

NIHSS = National Institutes of Health Stroke Scale (NIHSS)

Table 9.4 – Patient functioning according to the occurrence of successful recanalization and the type of recanalization.

Patient functioning		Recanalization			Type of recanalization		
		Yes (n=56)	No (n=42)	*P-value*	Spontaneous (n= 11)	Therapeutic (n=45)	*P-value*
Good General Functioning (mRS 0–2), n (%)	**48 hours**	13 (23.2)	2 (4.8)	0.012	1 (9.1)	12 (26.7)	0.426
	3 weeks	31 (55.4)	12 (28.6)	0.008	3 (27.3)	28 (62.2)	0.048
	12 weeks	37 (66.1)	17 (40.5)	0.012	4 (36.4)	33 (73.3)	0.032
	24 weeks	36 (64.3)	18 (42.9)	0.035	4 (36.4)	32 (71.1)	0.041
Good Hand Functioning (SULCS 8–10), n (%)	**48 hours**	22 (39.3)	5 (11.9)	0.003	3 (27.3)	19 (42.2)	0.498
	3 weeks	27 (48.2)	11 (26.2)	0.027	3 (27.3)	24 (53.3)	0.121
	12 weeks	32 (57.1)	12 (28.6)	0.005	3 (27.3)	29 (64.4)	0.041
	24 weeks	31 (55.4)	12 (28.6)	0.008	3 (27.3)	28 (62.2)	0.048

mRS = modified Rankin Scale; SULCS = Stroke Upper Limb Capacity Scale

Table 9.5 – Patient functioning at 12 weeks after stroke for patients with successful recanalization, according to patients' characteristics.

Characteristics	Good General Functioning (mRS 0 – 2)			Good Hand Functioning (SULCS 8 – 10)		
	Yes (n=37)	No (n=19)	*P-value*	Yes (n=32)	No (n=24)	*P-value*
Age, median (Q1; Q3)	68.0 (60.0; 75.0)	79.0 (64.0; 82.0)	0.016	68.5 (61.5; 75.0)	76.5 (64.0; 82.0)	0.047
NIHSS, median (Q1; Q3)	9.0 (6.0; 14.0)	17.0 (13.0; 23.0)	0.006	7.5 (6.0; 12.0)	17.0 (13.5; 22.5)	< 0.001
Female gender, n (%)	13 (35.1)	15 (78.9)	0.002	9 (28.1)	19 (79.2)	< 0.001
Atrial fibrillation, n (%)	16 (43.2)	11 (57.9)	0.299	19 (59.4)	10 (41.7)	0.189
Hypertension, n (%)	22 (59.5)	13 (68.4)	0.512	20 (62.5)	15 (62.5)	1.000
Cardioembolic stroke, n (%)	16 (43.2)	12 (63.2)	0.158	13 (40.6)	15 (62.5)	0.105
Therapeutic recanalization technique, n (%)	33 (89.2)	12 (63.2)	0.032	29 (90.6)	16 (66.7)	0.041

mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale (NIHSS); SULCS = Stroke Upper Limb Capacity Scale

PART D

CONCLUDING REMARKS

CHAPTER 10

INTEGRATIVE MODEL TO PREDICT UPPER LIMB FUNCTIONING AFTER STROKE

Determining upper limb functioning after stroke

In a time when there is a greater disparity of actions and opinions regarding each pathology, there is an increasing need to gather evidence that objectively support certain clinical decisions. Approximately 70% of medical decisions are found to be based on complementary diagnostic tests (imaging, laboratory test, etc.). Thus, in the context of PRM it is increasingly important to create protocols, guidelines, consensus statements; that is, to find a general objectively valid standard for the medical practices of the physiatrist.

This chapter does not aim to discuss this research project, but to present an original contribute to the field, by integrating all the works conducted in the context of this project. The overall discussion of each work in presented in the next chapter. This chapter is essentially a personal reflection on the methodology applied and the overall findings, in an attempt to make an original contribution to the scientific community. It is intended to generate clinical decision elements for physiatrists, from the rehabilitation program to implement, the goals to achieve, as well as the best approach to manage the expectations of the patient and caregiver. Thus, contributing to develop lines of action based on evidence-based medicine.

In order to get a better understanding of the foreseeable level of upper limb functioning after stroke, we build an integrative model that uses the several predictive factors established in these studies. Four main predictive factors were used in developing this model: Age, S100β, ASPECTS at 24h, and NIHSS at admission. Based on the results from above discussed studies, the following cut-offs for "upper limb functioning" (SULCS 4-10) at 12 weeks were used:

- Age: <69.5 years old
- S100β: <140.5 ng/L
- NIHSS: <13.5
- ASPECTS: >7.5

These cut-offs were selected since they were identified as predictors of functional capacity in the post-stroke period. Logistic regression techniques were used to estimate the probability of the patient showing upper limb functioning (i.e. SULCS 4-10) based on these four different predictors. A stepwise, Forward LR selection method was used. The results of logistic regression are presented in Table 10.1. Only S100β, Age, and NIHSS were considered for the final model; ASPECTS scores were removed according to the regression analysis methodology.

Table 10.1 – Logic regression to predict upper limb functioning at 12 weeks after stroke.

Predictors	β	SE	OR	95% CI	p-value
$S100\beta$ (< 140.5)	2.738	0.579	15.462	4.970 – 48.109	< 0.001
NIHSS (< 14)	2.647	0.582	14.113	4.510 – 44.167	< 0.001
Age (< 69.5)	1.445	0.537	4.242	1.479 – 12.162	0.007

Logistic regression model. For each predictor, the regression coefficient is presented (β), standard error for the coefficient (SE), odds ratio (OR), the corresponding 95% confidence interval, and finally the p-value.

The logistic regression model is statistically significant (χ^2 (3)=82.148; p<0.001). It is able to explain 62.4% (Nagelkerke R^2) of the variability in the dependent variable and correctly classifies 84.0% of cases. The model has a sensitivity of 87.7% (i.e. the model correctly classifies 87.7% of individuals who presented upper limb functioning at 12 weeks) and a specificity of 79.3% (i.e. the model correctly classifies 79.3% of individuals who presented no upper limb functioning at 12 weeks). Figure 10.1 shows the ROC curve for this model. This model has a good discriminative capacity with an AUC of 0.907 (CI 95% 0.858–0.957), which means the model has a 90.7% probability of correctly classifying cases in terms of upper limb functioning (here defined as SULCS 4-10).

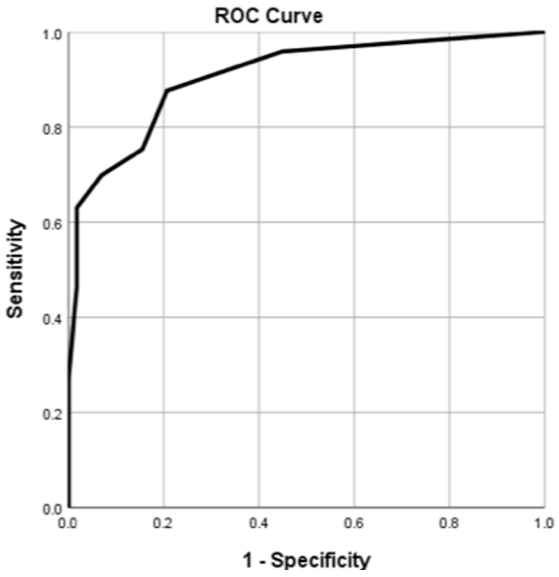

Figure 10.1 – ROC curve for the probability of upper limb functioning at 12 weeks.

Based on this integrative model, individuals with S100β at 48 hours <140.5 ng/L are more likely to have upper limb functioning at 12 weeks compared to those with levels ≥140.5 ng/L; individuals with NIHSS at admission <14 are more likely to have a upper limb functioning at 12 weeks compared to those with NIHSS ≥14; individuals <69.5 years-old are more likely to have upper limb function at 12 weeks than those ≥69.5 years-old.

The analytical expression of the model used to estimate the probability of upper limb functioning at 12 weeks is as follows:

$$\hat{\pi} = \frac{1}{1 + e^{-(-2.304 + 2.738 * S100\beta + 2.647 * NIHSS + 1.445 * age)}}$$

This analytical expression can be used to specifically calculate the probability showing upper limb functioning 12 weeks after stroke, based on the specific data of a particular patient (using the

patient characteristics for age, S100β, and NIHSS). Thus, these results can be used to establish a tailored probability of showing upper limb functioning for each patient.

For an approximate estimate that can be easily applied in clinical practice settings, Table 10.2 can be used. This table contains all the possible combinations of the initially defined cut-offs, presented in an easy to use fashion. The following probabilities of upper limb functioning are reached:

Table 10.2 – Estimating the probability of upper limb functioning (SULCS 4-10) at 12 weeks after stroke.

S100*β*	NIHSS	Age	Probability of upper limb functioning (SULCS 4-10) at 12 weeks (%)
+	+	+	98.93
+	+	–	95.61
+	–	+	86.75
–	+	+	85.67
+	–	–	60.69
–	+	–	58.49
–	–	+	29.75
–	–	–	9.08

+ S100β<140.5; NIHSS<14; Age<69.5 – S100β≥140.5; NIHSS≥14; Age≥69.5

Interpretation of this model

This model is aimed at predicting upper limb functioning based on SULCS assessment score.

SULCS is one of the most well-suited instruments for recovering stroke patients since it includes items evaluating both basic upper limb functioning (i.e. activities that require reduced or no hand functioning) and more demanding upper limb functioning (i.e. activities that require intensive distal functioning). SULCS assessments are short (approximately six minutes) and are based on 10 specific activities that are related to the patients' ADLs. Three items (SULCS 1–3) evaluate proximal functioning (in which there is no active function from the hand and fist), four items (SULCS 4–7) evaluate functioning that requires basic control of the fist and fingers, and three items (SULCS 8–10) evaluate advanced distal functioning. Therefore, in this model the probability of upper limb functioning (SULCS 4–10) is the probability of patients showing hand functioning at 12 weeks from basic control of the hand and fist to advanced functioning including the fingers.

This scale was chosen in detriment of others because, according to the ICF, upper limb capacity can be defined as "the execution of a task or action involving the upper limb by an individual in a 'standardized' environment [19]." Upper limb capacity differs from upper limb performance with respect to the environment in which the task or action takes place; capacity relates to a "standardized" and "optimum" environment (e.g, a test environment), whereas performance relates to the "current"

environment (e.g, home environment). Other upper limb capacity scales hade several limitations, some require sufficient hand function and therefore cannot suitably assess basic upper limb capacity in severely affected patients [149–152]. In the post-stroke period this is particularly relevant because a substantial portion of patients show poor hand function. Other scales have tasks that are not specifically related to upper limb functions and assess functions such as muscle strength and joint mobility [153–158], thus these are not purely upper limb assessment scales.

Example of interpretation of the model:

For a patient who has a S100β level of 130 ng/L, an NIHSS at admission of 20 and is 45 years-old, the probability of having upper limb functioning at 12 weeks is 86.75%. In this case, according to the previous table, we have the combination S100β +, NIHSS –, Age +, and therefore, the corresponding probability is 86.75%.

On the other hand, for a patient who has a S100β level of 150 ng/L, an NIHSS at admission of 15 and is 71 years-old, the probability of having hand functioning at 12 weeks is 9.08%. In this case, according to the previous table, we have the combination S100β –, NIHSS –, Age –, and therefore, the corresponding probability is 9.08%.

In conclusion, this integrative model can provide valuable insight when establishing medium-term prognosis for the upper limb in the post-stroke period. This information can then be used to develop a tailored rehabilitation approach aimed at ensuring that patients reach their maximum potential. Thus, this predictive model can be integrated by the scientific/clinical community to support best practices in clinical care.

It will enable clinicians to identify the patient's potential for recovery in the very early stages of stroke by defining long-term severity. Given the 12-week recovery window in these patients and the constant need to invest in patient recovery it is crucial for the clinician to define the best rehabilitation strategies individually for each patient, allowing for the best allocation of resources. For example, for a patient with a dominant side plegia and a low probability of functional hand recovery at 12 weeks, it is crucial to define this prognosis early, assume the severity of the situation, and make the decision to provide lateralization change training from the beginning. This is one of the most difficult decisions for the clinician and it is often a difficult consensus with the patient and caregivers. There is a great need for objective instruments to support this clinical decision. This approach should not neglect the affected hand, providing rehabilitation care not from a functional perspective, but from a perspective of tone control and correct positioning.

This model was essentially studied to define the functional capacity of the upper limb, but its extension, although not direct, could provide some degree of approximation for overall functioning. Upper limb recovery demonstrated to be highly correlated with neurological/functional recovery, although in specific cases patients can show an overall high degree of functionality, with significant upper limb impairment. Still, it should be noted that functional recovery will always be a multifactorial, heterogeneous and patient-specific process, but such models can provide greater insight into the specific recovery potential of each patient than current clinical assessments.

We are entirely aware that this model—in its current formulation and with the currently available supporting evidence—is intrinsically limited. Still this exercise can contribute with useful insight to the clinical management and rehabilitation of stroke patients. More importantly, it establishes a more solid base for future research in the search for robust serum biomarkers of functional outcomes in stroke patients.

CHAPTER 11

OVERVIEW AND CONCLUSIONS

Overview and conclusions

In the scientific community there is an increasing interest in developing highly accurate predictors of health and disease outcomes. In the context of rehabilitation, developing such markers can add immense value when tailoring rehabilitation programs according to specific patient needs.

Biomarkers and neuroimaging techniques have intrinsic prognostic value in the management of acute stroke patients, from diagnosis, to therapeutic decision, follow-up, functional prognosis and prevention. In terms of functional prognosis in particular, the assessment of the volume of brain lesion through neuroimaging techniques, is correlated with functional prognosis. High levels of S100β in peripheral blood also show a strong correlation with hemorrhagic transformation and worse prognosis [159, 160]. However, despite the prognostic value of such isolated markers, there is a need to integrate insights from various sources to establish more accurate prognostic models [161, 162], and this was the main goal of this thesis.

In order to establish such predictive models, there is a need to better understand the complex cascade of events leading to stroke. Ischemic and hemorrhagic strokes share some similarities in the pathophysiological pathways leading to the acute events, but also have major differences. Figure 11.1 summarizes the series of events occurring in ischemic stroke, which was the focus of study in this work.

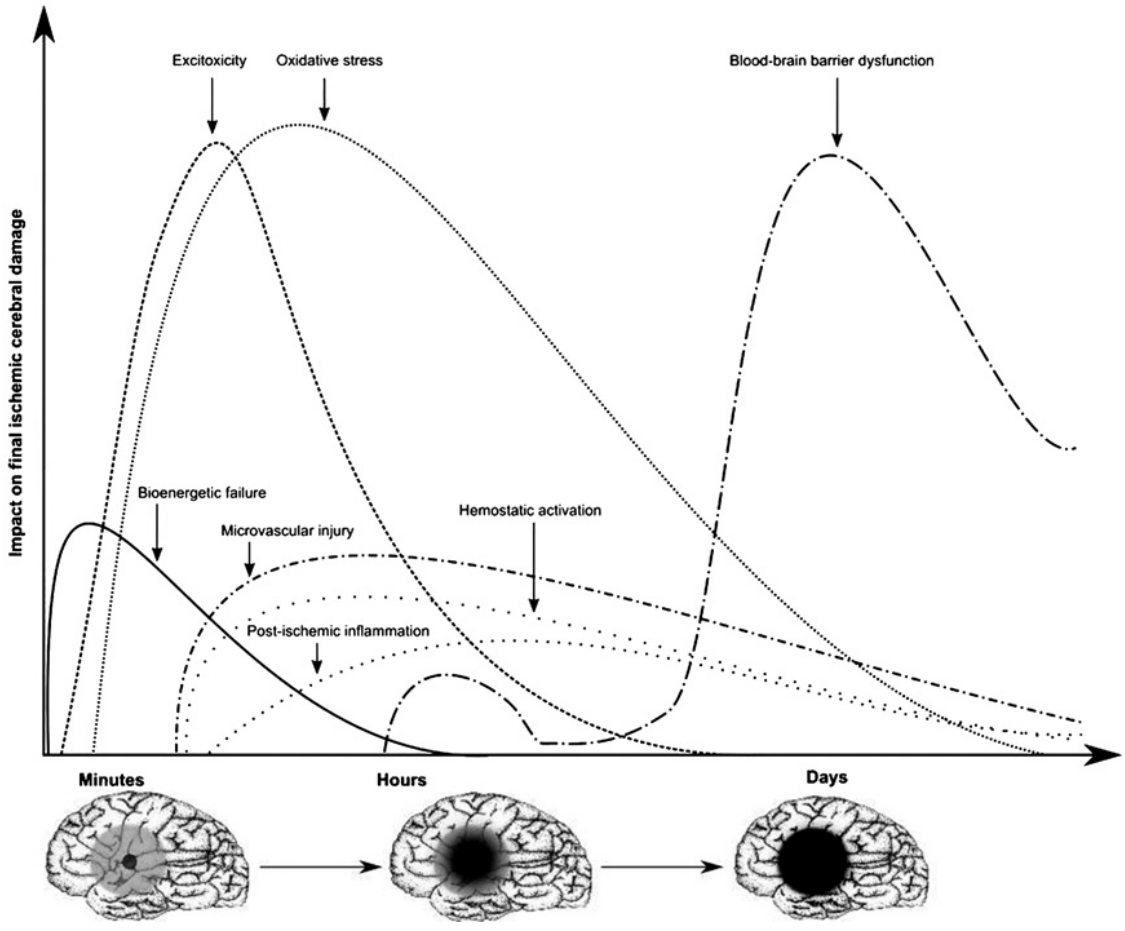

Figure 11.1 – Timing of events in ischemic stroke.
Adapted with permission from: Brouns, R. & De Deyn, P. P. (2009). Clin. Neurol. Neurosurg. 111, 483–495.

The continuous search for a better understanding of this phenomenon will allow the identification of more and better predictive factors of long-term functioning in stroke patients. This will provide valuable data to support the development and optimization of better rehabilitation programs, ensuring better resource allocation and improving patient outcomes.

After stroke, the probability of achieving a level of functionality >60 in the Barthel Index is inversely proportional to the motor, sensorial and visual impairments presented by the patient as illustrated in Figure 11.2.

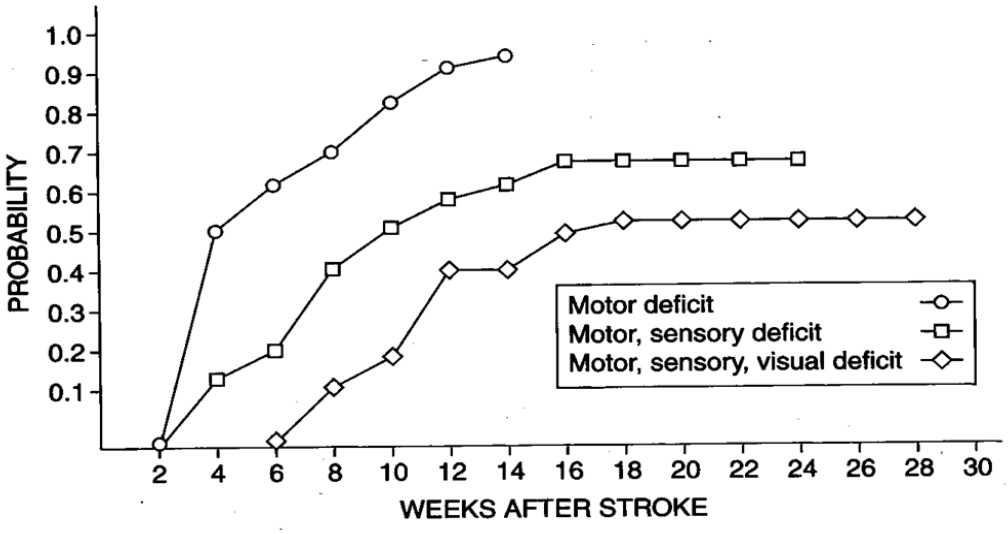

Figure 11.2 – Probability of achieving functioning >60 in the Barthel Index after stroke.
Adapted with permission from: Han L, Law-Gibson D, Reding M. Stroke. 2002;33(7):1920-1924.

The level of neurological recovery after stroke is dependent on a complex physiological process involving the activity of penumbra cells, recovery of diaschisis, and the activation of secondary circuits. Functional recovery depends on the level of control of mobility sequelae, motor and sensitive stimulation, exercise in activities of daily living, and reconditioning [163, 164].

A later phase in the rehabilitation process should be considered (after >24 weeks), when it is crucial to continue neuromuscular rehabilitation, exercise in both simple and instrumental ADLs, adapt the home environment, adapt the overall involving social environment, and adapt the professional context, if applicable. In this context, of course, the operative variables in stroke rehabilitation need to be considered, including age, etiology, localization, extension and severity, neurological deficits, sociocultural and economic condition, and family dynamics [2, 3, 26].

Predictive capacity of acute phase biomarkers in terms of functional prognosis after stroke

We hypothesized that biomarker levels, including CPR, D-Dimer, and fibrinogen at hospital admission, and S100β levels in peripheral blood at 48 hours post-stroke are associated with acute stroke severity and predict functional outcome at 12 weeks. In this work, we established S100β in peripheral blood as a reliable predictor of functional outcome 12 weeks after stroke, while other biomarkers typically used to predict vital outcome (including CRP, D-Dimer, and fibrinogen) were not strongly

associated with functional outcome. Additionally, S100β levels in peripheral blood measured in the acute phase of stroke (48 hours) appear to be a stronger predictor of functionality at 12 weeks than acute NIHSS scores. Peripheral blood levels of S100β reflected the severity of stroke and predicted functional prognosis, with levels ≥140.5 ng/L suggesting low functionality at 12 weeks. These findings and their implications are thoroughly discussed in Chapter 6.

S100β can, therefore, be used as a marker of disease in stroke patients in the acute phase. More studies are needed, with larger samples, focusing on the predictive value of S100β as a biomarker of neuroglia degradation. Translating these research findings to actual clinical practice, in which S100β assays will be easily accessible, is a major challenge that should be tackled at soon as possible.

Relationship between clinical condition at admission/ acute upper limb functioning and medium- to long-term functioning

We hypothesized that patients with worse clinical condition at hospital admission (measured through NIHSS) and with worse upper limb function at 48 hours (measured through SULCS) will present worse functional outcomes at 12 and 24 weeks after stroke. When assessing a panel of neuroimaging, serum, and clinical markers as predictors of upper limb functioning 12 weeks after stroke, ASPECTS score ≥8 within 24 hours of hospital admission and serum levels of S100β protein <140.5 ng/L at 48 hours after hospital admission were found to predict better upper limb functioning 12 weeks after stroke. Conversely, advanced age was significantly associated with worse upper limb functioning 12 weeks after stroke.

Upper limb functioning measured in the acute phase of stroke (48 hours) was strongly correlated with overall functioning and upper limb functioning after stroke both in the short- and medium-term (3 and 12 weeks). These findings suggest that SULCS in the acute phase of stroke can provide valuable insight for medium-term functional recovery, which warrants investigation in future studies. These findings and their implications are further discussed in Chapter 7.

Functional gains after stroke: the importance of the first 12 weeks

We hypothesized that the most relevant functional gains occur within the first 12 weeks after the acute event, which provides an important window of action for patient recovery. In this work, we confirmed that neurological and functional recovery follow a comparable trend until 12 weeks, as illustrated in Figure 11.3. However, after this point, neurological recovery plateaus but there is still observable progression in functional (at both a general level of functioning as well as specifically upper limb functioning), motor and cognitive capacity as measured by functional assessment scales. These findings lead us to conclude that further studies assessing the recovery of stroke patients should go beyond 24 weeks in duration. Additionally, better measurement instruments specifically designed for this pathology should be introduced to allow the identification of potential functional gains that would otherwise remain unidentified. These findings and their implications are further discussed in Chapter 8.

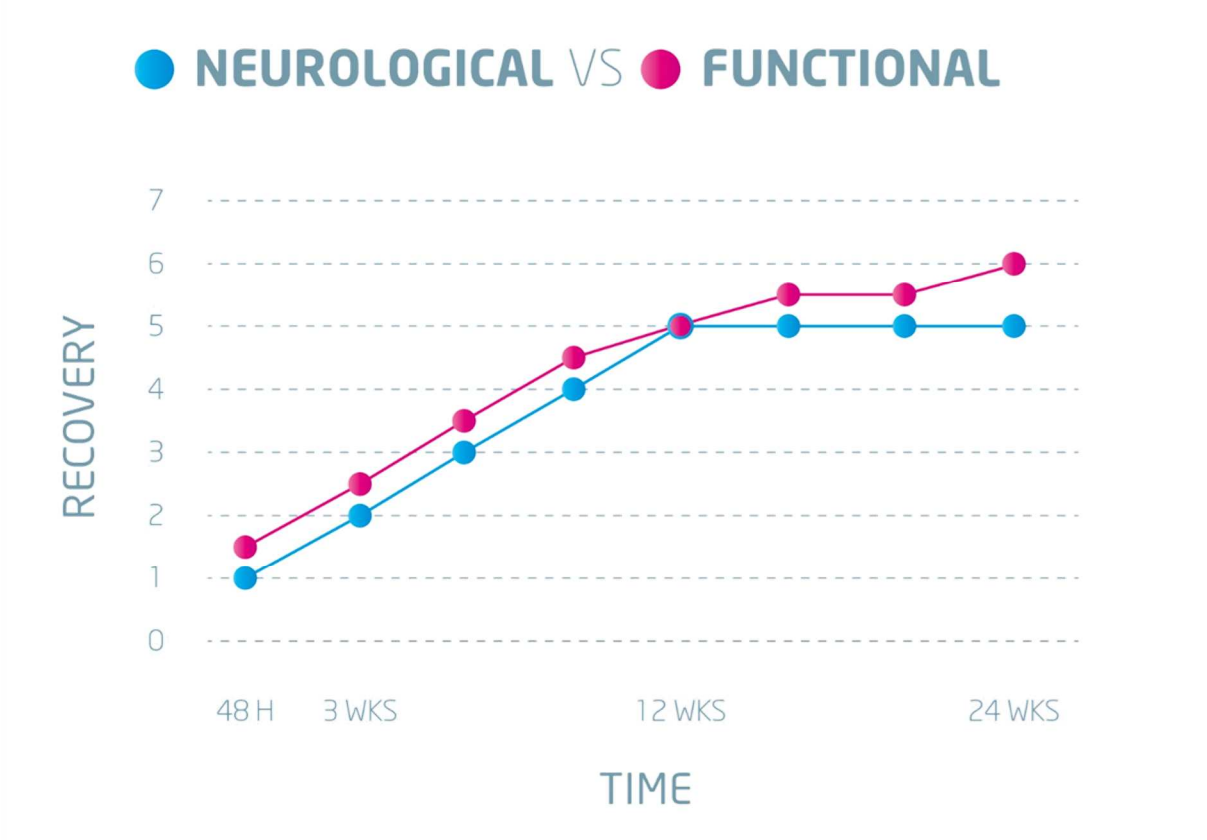

Figure 11.3 – Neurological and functional recovery after acute ischemic stroke.

Source: copyright is with the principal investigator. Illustrative figure created with data from this population showing the expected evolution of neurological/ functional recovery after stroke. Presented at: 12th International Society of Physical and Rehabilitation Medicine (ISPRM), 2018 Paris.

Patients with lesions in the MCA present, from a clinical point of view, hemiplegia with brachial predominance. There is a need to evaluate and recover the upper limb, defining assessment scales that are specific and sensitive to the neurological deficits, as well as define an adequate rehabilitation program that includes the expected timings for recovery.

This assessment by the clinician will define, in addition to the rehabilitation program, the need to continue the rehabilitation program in search for functional gains in the upper limb, or in alternative, define from a clinical standpoint the permanent non-functioning of the upper limb and consider the change in laterality as the main goal. This challenging clinical decision will allow the patient to more quickly recover functioning and also allows for better management of expectations, since managing patient expectations is one of the main challenges for clinicians. Rehabilitation is, thus, the search to minimize the difference between patient expectations and, actually, achievable functional capacity.

Since functional recovery can occur even after the period of neuroplasticity and neurological recovery, the rehabilitation program for stroke patients should be comprehensive and intensive aiming to obtain functional gains (motor and cognitive) to the furthest degree possible and to maintain this level of functioning over time.

Recanalization in the first 12 weeks: volume of the lesion and functioning

We hypothesized that recanalization, either spontaneous or therapeutic, in the first 24 hours post-stroke reduces the volume of brain lesion and, consequently, patients have better functional prognosis (both in terms of general functioning and, specifically, upper limb functioning). In this work we confirmed that recanalization, either spontaneous or therapeutic, has a positive impact on patient functioning after acute ischemic stroke, both in terms of general functioning and, specifically, upper limb functioning. Among patients who underwent a recanalization procedure, a NIHSS score at admission ≥17 predicted low general functioning at 12 weeks—measured through mRS—and NIHSS scores at admission ≥14 predicted no hand functioning at 12 weeks—measured through SULCS—despite the use of a recanalization technique. These findings and their implications are further discussed in Chapter 9.

These results emphasize that the clinical condition of the patient in the first 48 hours is determinant to achieve good hand functioning. This demonstrates the demanding endeavor that is upper limb functioning and its extensive cortical representation.

Biomarkers, neuroimaging and demographic factors: developing a predictive model of functioning to support clinical decisions

With this work we were able to build an integrative model that can provide valuable insight when establishing medium-term prognosis for the upper limb in the post-stroke period. This information can then be used to develop a tailored rehabilitation approach aimed at ensuring that patients reach their maximum rehabilitation potential.

The model uses a combination of 3 different predictors, including S100β, age, and NIHSS. Depending on the combination of these factors a probability of upper limb functioning at 12 weeks can be established, as illustrated bellow in Table 11.1.

Table 11.1 – Integrative model to predict the probability of upper limb functioning (SULCS 4-10) at 12 weeks after stroke.

S100*β*	NIHSS	Age	Probability of upper limb functioning (SULCS 4-10) at 12 weeks (%)
+	+	+	98.93
+	+	–	95.61
+	–	+	86.75
–	+	+	85.67
+	–	–	60.69
–	+	–	58.49
–	–	+	29.75
–	–	–	9.08

+ S100β<140.5; NIHSS<14; Age<69.5 – S100β≥140.5; NIHSS≥14; Age≥69.5

With this tool, considering the initial factors, and according to this integrative model, it will be possible to support the clinician in defining a likely functional prognosis, and then better define the best treatment and rehabilitation approach for each patient. This model can be a valuable support tool for clinicians in their daily practices, allowing a better management of scarce resources by potentiating the recovery of patients with a high recovery potential.

Future perspectives

The need to understand the pathophysiology of stroke in the early hours is of crucial importance and may help in the search for more and better markers of diagnosis and prognosis. The translation of basic and clinical science will be of crucial importance, and this is the proposed function of this work.

The search for more and better predictors of patient functioning after acute stroke will provide valuable information to support the development and optimization of rehabilitation programs, allowing better allocation of resources, and ultimately improving patient outcomes.

The quest to improve rehabilitation programs has been constant and instrumental improvements have already been seen. The resources that allow better recovery of upper limb functioning have been growing over the years and include techniques such as repetitive transcranial magnetic stimulation (rTMS), virtual reality and robotic therapy among others [124–128].

The patient recovery process should start shortly after stroke and comprises several steps as illustrated in Figure 11.4.

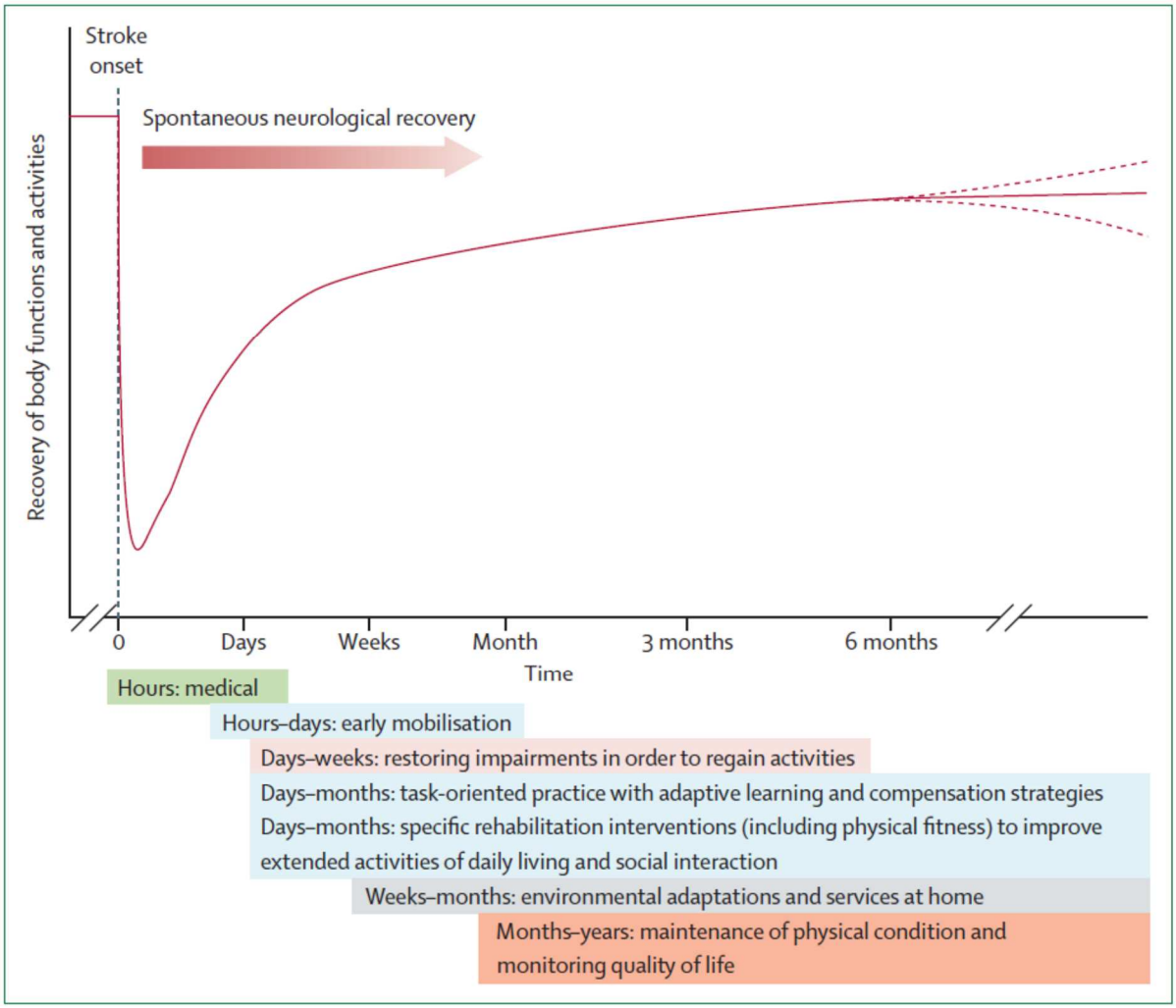

Figure 11.4 – Steps in the rehabilitation of stroke patients.
Adapted with permission from: Langhorne P, Bernhardt J, Kwakkel G. Lancet. 2011;377(9778):1693-1702.

It is always important to note that the capacity of patients to achieve rehabilitation goals depends on their motivation, social-familiar support and, above all, their cognitive status. The education and formalization of the caregiver can add value in maintaining gains and avoiding immobility sequelae after discharge from the rehabilitation program. This approach provides the best chances of patient integration and participation in society.

Participation in society should, actually, be seen as a goal for the rehabilitation of stroke patients. The ability of the individual to participate in society is often affected after stroke as a result of bodily impairments, which in turn limit the ability of the individual to perform normal activity. Even the presence of substantial gains in functioning during a rehabilitation program, the ability to participate in society should always be considered, since it can be highly dependent of personal, environmental, contextual factors specific to each patient.

When identifying potential knowledge gaps in the rehabilitation of stroke patients, there is in general a need to extend follow-up studies beyond 24 weeks. An increasing number of studies has assessed stroke patients in such timeframes, highlighting a potential for functional improvement in later stages (up to 2 years post-stroke). Longer-term studies should ideally use newly-developed sensitive and specific functional assessment scales that are more appropriate to the pathology in question, as well as the social and cultural issues involved [93, 153, 165–168].

In this study, S100β was particularly identified as a strong predictor of functional outcomes after stroke. Therefore, the clinical utility of S100β as a predictor of functional recovery after-stroke should be emphasized in clinical practice, though large-scale studies with longer follow-up periods should be conducted to further validate the use of this biomarker.

This study allowed us to contribute to clinical research in the context of PRM and highlight the need and added value of translational science, which is paramount in building predictive models that integrate the laboratory, clinical and functional components.

We will thus enter into another dimension of PRM research that has specificities regarding its biopsychosocial dimension (heterogeneous samples, centered in the patient as a whole—holistically—but always supported in functioning). In this context, we highlight the imperative need to create working groups to develop more, new, and better predictive models in the most diverse areas of PRM, all based on patient functioning and, in this new era of PRM, having as the main objective the integration of patient participation [9].

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APPENDIX 1

PORTUGUESE VALIDATED SULCS SCALE

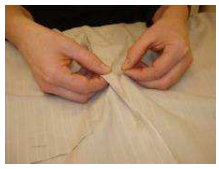
ESCALA DE CAPACIDADE DO MEMBRO SUPERIOR APÓS ACIDENTE VASCULAR CEREBRAL (SULCS)

PONTUAÇÃO **0** = o/a doente é incapaz de executar a tarefa da forma descrita
1 = o/a doente é capaz de executar a tarefa da forma descrita
Apêndice A Instruções gerais e lista de materiais do teste para a SULCS
Apêndice B Formulário para as tarefas 9 e 10

Nota:
Opção 1: comece o teste com a tarefa 1 e continue daí para a frente. Quando ***não puderem*** ser executadas 3 tarefas consecutivas, o teste deve ser parado. Cada item restante é pontuado com 0.
Opção 2: comece o teste com a tarefa 10 e continue daí para trás. Quando ***puderem*** ser executadas 3 tarefas consecutivas, o teste deve ser parado. Cada item restante é pontuado com 1.

		Descrição	Imagem	Pontos
	O quê	**Usar o antebraço para apoio enquanto está sentado/a**		
	Como	**Esticando todo o corpo, apoiando-se no antebraço do membro afetado**		
	Preparação	O/A doente está sentado/a a uma mesa. O antebraço afetado está pousado na mesa, paralelamente à borda do lado em que o/a doente está sentado/a. É colocada uma		☐
1		caneta em cima da mesa, em frente ao cotovelo afetado e longe o suficientemente longe para que, para lá chegar, seja necessário estender completamente o braço não afetado e movimentar a parte superior do tronco.		
	Tarefa	O/A doente estica-se para pegar na caneta com a mão não afetada. O antebraço afetado é usado como apoio.		
	Nota	O braço afetado não pode mover-se quando o/a doente se estica para a frente para pegar na caneta.		
	O quê	**Apertar um objeto entre o tronco e o braço**		
	Como	**Pressionando o membro afetado firmemente contra o lado do corpo**		
	Preparação	O/A doente está em pé (sentado/a, se necessário) junto a uma mesa. Em cima da mesa		☐
2		está uma revista dobrada longitudinalmente. O membro afetado está naturalmente caído ao lado do corpo.		
	Tarefa	O/A doente pega na revista com a mão não afetada e aperta-a entre o tronco e o braço afetado.		
	Nota	A revista tem de ser segurada firmemente durante 10 segundos. O clínico certifica-se disso, se necessário, puxando ligeiramente a revista.		
	O quê	**Fazer deslizar um objeto sobre uma mesa estando sentado/a**		
	Como	**Usando movimento deslizante controlado da mão afetada**		
	Preparação	O/A doente está sentado/a a uma mesa. A mão afetada está sobre a mesa por cima de		☐
3		uma toalha de mesa dobrada em quatro, com a palma virada para baixo e os dedos apontando para a frente.		
	Tarefa	O/A doente empurra a toalha para a frente sobre a mesa		
	Nota	O cotovelo tem de estar em extensão pelo menos 160º e poderá ser levantado da mesa. Os dedos não precisam de estar completamente estendidos		
	O quê	**Desenroscar (parcialmente) uma tampa**		
	Preparação	O/A doente está sentado/a a uma mesa, ambos os braços sobre a mesa. Um frasco de doce fechado com uma tampa plástica de desenroscar está pousado na mesa à frente		☐
4		do/a doente, a 15cm.		
	Tarefa	O/A doente segura o frasco firmemente sobre a mesa com a mão não afetada e, usando a mão afetada, desenrosca a tampa pelo menos um quarto de volta.		
	Nota	O frasco deve permanecer no mesmo lugar na mesa e não se pode rodar.		
	O quê	**Pegar num copo de água e beber**		
	Preparação	O/A doente está sentado/a a uma mesa, ambos os braços sobre a mesa. Um copo, meio cheio de água, está pousado na mesa à frente do/a doente, a 15cm.		☐
5	Tarefa	O/A doente pega no copo, levantando-o com a mão afetada, bebe e volta a colocar o copo na mesa sem entornar.		
	Nota	A mão não afetada não é usada.		

ESCALA DE CAPACIDADE DO MEMBRO SUPERIOR APÓS ACIDENTE VASCULAR CEREBRAL

6	O quê	**Agarrar uma bola colocada num local elevado**		☐
	Preparação	O/A doente está em pé (sentado/a, se necessário) sem outro apoio ao seu alcance. O clínico mantém uma bola de ténis na frente e acima do ombro afetado de tal forma que o/a doente tem de estender totalmente o braço afetado e de o elevar ± 120º para agarrar a bola de ténis.		
	Tarefa	O/A doente toca na bola e pega-lhe com a mão afetada.		
7	O quê	**Pentear o cabelo**		☐
	Preparação	O/A doente está em pé (sentado/a, se necessário) junto a uma mesa. O pente está pousado na mesa, ao seu alcance.		
	Tarefa	O/A doente penteia o cabelo com pelo menos 2 movimentos na parte de cima e de cada lado da cabeça.		
	Nota	A cabeça deve ser mantida levantada. O/A doente pode chegar aos lados partindo de cima ou de lado. Quando a situação clínica é menos adequada a este teste, deve ser feito um movimento "faz de conta".		
8	O quê	**Apertar botões**		☐
	Como	**Usando as 2 mãos**		
	Preparação	O/A doente está sentado/a a uma mesa. Uma camisa de homem está pousada na mesa, precisamente na frente do/a doente. O colarinho está na parte de cima, virado para cima. O botão de cima está apertado, todos os outros estão desapertados. O/A doente aperta 4 botões no espaço de 60 segundos, usando ambas as mãos.		
	Tarefa	Os dedos afetados devem ser usados, para segurar o tecido ou o botão ou para manter aberta a casa do botão.		
	Nota			
9	O quê	**Escrever**		☐
	Como	**Ver Apêndice B**		
	Preparação	O/A doente está sentado/a a uma mesa. A folha de papel do Apêndice B está pousada na mesa à frente do/a doente, a 15cm. Uma caneta está pousada na folha de papel.		
	Tarefa	*(versão 1: o lado afetado não é o lado dominante)* O/A doente pega na caneta e desenha 3 círculos entre os dois círculos da folha, sem tocar nas bordas dos círculos impressos ou de qualquer círculo já desenhado.		
	Nota	Explique na íntegra as instruções e sugira ao/à doente que comece perto do círculo interno. O/a doente pode deslocar a folha de papel.		
	Tarefa	*(versão 2: o lado afetado é o lado dominante)* O/A doente pega a caneta e escreve o seu primeiro e último nome de forma legível, na sua própria caligrafia, entre as linhas.		
	Nota	O/a doente pode deslocar a folha de papel.		
10	O quê	**Manipular moedas**		☐
	Como	**Ver Apêndice B**		
	Preparação	O/A doente está sentado/a a uma mesa. A folha de papel do Apêndice B está pousada na mesa, precisamente na frente do/a doente. Em cima da mesa está uma moeda de 50 cêntimos, uma moeda de 2 cêntimos e uma moeda de 1 cêntimo (ou seus equivalentes em tamanho e peso). O antebraço afetado está pousado na mesa com a palma da mão virada para cima. Usando a mão não afetada, o/a doente coloca as moedas na mão afetada.		
	Tarefa	O/A doente manipula as moedas com a mão afetada, uma de cada vez, até ficarem entre as pontas do polegar e do indicador e coloca-as nas posições que lhes estão destinadas na folha.		
	Nota	Não importa por que ordem as moedas são colocadas nos lugares que lhes estão destinados. Durante a manipulação, o antebraço deve estar pousado sobre a mesa.		

PONTUAÇÃO TOTAL ☐

APÊNDICE A: INSTRUÇÕES GERAIS E LISTA DE MATERIAIS PARA EXECUTAR OS TESTES DO SULCS

Instruções e explicação

1. As 10 tarefas da lista estão por ordem de dificuldade e complexidade.
2. As tarefas são executadas em pé ou sentado/a. É permitido alterar a ordem das tarefas por razões práticas.
3. Todas as tarefas devem ser executadas sem ajuda.
4. É importante registar se a tarefa pode ser executada de acordo com as instruções. (capaz/incapaz), não a qualidade com que é executada.
5. Se necessário, é permitido repetir as instruções ou demonstrar a tarefa.
6. Pode decidir se começa pela tarefa 1 ou pela tarefa 10 fazendo antecipadamente uma avaliação do nível de capacidade do membro superior. Comece pela tarefa 1 para baixa capacidade e pela tarefa 10 para capacidade elevada.

Materiais do teste

- Uma mesa regulável em altura.
- Uma cadeira.
- Uma caneta.
- Uma revista mais ou menos de tamanho A4 (±210g) dobrada ao meio no sentido longitudinal.
- Uma toalha de chá.
- Um frasco de doce vazio, ±400g, com uma tampa plástica de desenroscar (±20mm de altura, tampa com diâmetro ±77mm). A tampa fechada e o frasco são marcados com uma caneta marcador para que cada vez que o frasco é fechado, como seria após o uso normal, as marcas fiquem alinhadas (objetivo: assegurar que o grau de dificuldade é o mesmo cada vez que o teste é realizado).
- Um copo alto (±55mm de diâmetro, ±150mm de altura).
- Uma bola de ténis.
- Um pente.
- Uma camisa de homem.
- Um cronómetro.
- Três moedas de diferentes tamanhos: uma moeda de 50 cêntimos (±23mm de diâmetro), uma moeda de 2 cêntimos (± 17mm de diâmetro) e uma moeda de 1 cêntimo (±15mm de diâmetro), ou seus equivalentes em tamanho e peso.
- Apêndice B.

APÊNDICE A: FORMULÁRIO PARA AS TAREFAS 9 E 10

TAREFA 9

Nota: Esta tarefa só é executada se o lado dominante estiver afetado

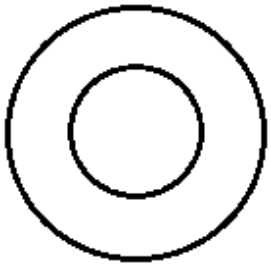
Escreva o seu nome na sua própria caligrafia entre as duas linhas, sem transpor as linhas:

_____

_____

Nota: Esta tarefa só é executada se o lado não-dominante estiver afetado

Desenhe três círculos entre os círculos impressos, sem tocar nas bordas do círculo impresso ou de qualquer círculo já desenhado:



TAREFA 10

Coloque as moedas nas posições corretas:

50 cêntimos **2 cêntimos** **1 cêntimo**